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DIAGNOSTIC FEATURES OF PANCREATIC DISEASE

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Acute inflammatory lesions of the pancreas commonly are misdiagnosed, and chronic pancreatic disorders frequently are unrecognized until late in their course of development. One factor contributing to this situation is a lack of sufficient awareness of the pancreas and its disorders. Another factor is a widespread impression that diagnostic approaches to the pancreas are sharply limited. This presentation is intended to indicate that the clinical, laboratory, and roentgenologic expressions of pancreatic disease are surprisingly many. It is hoped that a review such as this will serve to stimulate interest in the gland and the diseases affecting it. It is further hoped that with increased awareness of the pancreas and wider use of the diagnostic approaches, pancreatic diseases will be recognized oftener and earlier.

CLINICAL FEATURES

Pain.—Pain sensation is transmitted bilaterally from the pancreas along visceral afferent fibers accompanying the splanchnic nerves on both sides.[1] In addition, pain may be conducted along somatic afferent pathways because most of the anterior surface of the pancreas is covered by parietal peritoneum. The distribution of pain arising from the pancreas depends largely on the portion of the gland affected. This has been clearly demonstrated by Bliss and his associates.[2] These workers inserted electrodes into various portions of the pancreas in a group of patients undergoing elective biliary tract surgery. They observed that when the head of the pancreas was electrically stimulated, the pain that resulted was distributed over the right epigastrium; stimulation of the body of the pancreas produced pain in the midepigastric region; stimulation of the tail gave rise to pain in the left lower epigastric region and sometimes in the left lower quadrant. When all parts of the gland were stimulated simultaneously, band-like pain was felt across the epigastrium with radiation to the back. Factors other than the site of involvement also determine the pain patterns of pancreatic disease. No typical pattern can be defined, but certain features are characteristic.[3] The intensity of pain varies with the extent and degree of inflammatory or neoplastic change in and about the pancreas. Pain may be excruciating in cases of acute pancreatic necrosis; while it is not as intense in cases of lesser severity, it is apt not to respond promptly to ordinary therapeutic doses of opiates. In chronic pancreatitis and in cancer of the pancreas, pain is usually mild to moderate in severity but there may be episodes of pronounced severity. Pancreatic pain is variably described by patients but is generally constant and often said to be a boring type of pain. Posterior radiation of the pain and exacerbation at night, or at other times when the patient is supine, are highly characteristic. Flexion of the trunk often provides some degree of relief. Patients whose pain arises from the pancreas, especially those with cancer, typically seek relief by sitting up, bending forward, or walking about with their trunks flexed and their hand pressed against the epigastrium.

Jaundice.—Jaundice occurring in patients with pancreatic disorders is usually considered a result of secondary obstruction of the major extrahepatic ductal system because of edema, inflammation, compression or infiltration, and fixation. The possibility of coexistent primary biliary tract disease also deserves to be given thought, particularly when jaundice is a feature of acute pancreatitis. Another mechanism to be considered is intrahepatic obstruction resulting from pericholangitis. That this may occasionally occur in man is suggested by the appearance of hyperbilirubinemia in some dogs with experimentally induced acute pancreatitis; the extrahepatic bile ducts of these dogs were found to be patent, but their livers showed pronounced pericholangitis.[4] Jaundice is one of the outstanding features of cancer of the pancreas, especially when the head of the pancreas is involved. Indeed, jaundice appearing in the absence of pain is a classical expression of cancer of the pancreas. It is still insufficiently appreciated, however, that pain in patients with cancer of the pancreas occurs with a frequency even exceeding that of jaundice.[3c] Jaundice without pain, therefore, while diagnostically important when present, does not occur in most patients with cancer of the pancreas.

Weight Loss.—Patients with chronic affections of the pancreas that are attended by wide destruction of pan-

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creatic tissue or obstruction of the pancreatic ducts commonly lose considerable body weight. Not only is the degree of weight loss uncommonly great but the rapidity with which the loss takes place is impressive. The latter is true particularly in cancer of the pancreas.[5e]

Emotional Derangements.—Behavior disturbances and personality derangements may be detected surprisingly often in patients with pancreatic disease of various types.[5] The most striking emotional alterations, however, occur in those with cancer.[5a] The symptoms seen in patients with cancer consist principally of anxiety and depression, with insomnia, crying spells, and conviction of imminent physical danger. At times such disturbances in behavior may be among the earliest manifestations of the disease. It seems warranted, therefore, to suspect the possibility of cancer of the pancreas in any patient with unexplained abdominal pain who also displays emotional disturbances featuring anxiety or depression. Far too often, abdominal pain in a person with nervous symptoms such as these tends to be regarded merely as an expression of an underlying psychosomatic disturbance; only when jaundice makes a belated appearance, is its significance fully appreciated.

Multiple Venous Thromboses.—Multiple venous thromboses occur much more often in cases of carcinoma of the body and tail of the pancreas than in cases of carcinoma of other organs.[6] Carcinoma of the pancreas, particularly when restricted to the body and tail, may also be associated with a migratory thrombophlebitis. The latter is distinguished by its persistence, by the great number of veins involved, and by the tendency toward recrudescence in previously involved segments.[7] It is to be emphasized, therefore, that diagnosis of carcinoma of the body or tail of the pancreas should be considered whenever multiple venous thromboses or migratory thrombophlebitis are encountered in an older person, for either of which no other satisfactory causes can be found.

Gallbladder Distention and Pancreatic Mass.—Palpable distention of the gallbladder is one of the traditional physical features of cancer of the pancreas. A distended gallbladder may be felt by clinical examination in about half the patients with cancer of the pancreas attended by jaundice.[8] At operation or at autopsy, however, the percentage of cases of distended gallbladders is even greater. This indicates that, in conformity with Courvoisier's law, detection of an enlarged, nontender gallbladder in a patient with obstructive jaundice may be regarded as evidence favoring neoplastic obstruction of the extrahepatic bile ducts. Failure to detect a distended gallbladder on physical examination, on the other hand, does not exclude this diagnosis. Anesthesia may be used intravenously in doubtful cases to relax the abdominal wall and facilitate examination.[9] The deep, retroperitoneal location of the pancreas handicaps ordinary physical examination, but anesthesia induced intravenously may here again allow the examiner to detect a mass not otherwise palpable.[9] When a mass is detectable in the region of the epigastrium, the fact that it is movable does not exclude the pancreas as the site of origin. The pancreas, and tumors or cysts that arise from it, may exhibit some degree of mobility.[10]

LABORATORY FEATURES

Impaired Carbohydrate Metabolism.—Phenomena characteristic of the diabetic state are often associated with inflammatory and destructive lesions of the pancreas. Transitory glycosuria and hyperglycemia are frequently seen in patients with acute pancreatitis.[11] With abatement of the acute process, glycosuria disappears and blood sugar values usually return to normal. In some cases, however, destruction is so great that permanent diabetes mellitus results.[12] Glycosuria and hyperglycemia may also be found during acute exacerbations of chronic relapsing pancreatitis.[12b] In the intervals between acute attacks, latent diabetes may be demonstrated in some of these patients by an abnormal glucose tolerance test. Overt and permanent diabetes mellitus is not infrequent in advanced stages of the disease, particularly when there is roentgenologically visible calcification of the pancreas. Impaired glucose tolerance with a diabetic type of response has progressively emerged as probably the most valuable single sign pointing to the pancreas in cases of carcinoma of the pancreas.[13] Glycosuria and hyperglycemia may also be displayed, but the over-all frequency of these alterations appears to be less than that of an impaired glucose tolerance test.[14] Diabetes mellitus in some cases antedates the development of cancer of the pancreas.[3e] Indeed, cancer of the pancreas appears not only to be more prevalent among patients with diabetes [15] but in at least two series of patients with diabetes [16] it was the outstanding form of cancer. These considerations make it clear that development of abdominal pain in a diabetic patient or, conversely, the appearance of a diabetic phenomena in a patient with abdominal pain should lead one strongly to suspect the possibility of pancreatic disease.

Serum Pancreatic Enzymes.—The most widely used and probably the most valuable single means for the recognition of acute pancreatitis is determination of serum amylase.[17] Serum amylase usually attains its greatest value within 24 hours of onset of acute pancreatitis. The duration of elevation varies, depending principally on the severity of the process; in cases of acute pancreatic edema the amylase level usually returns to normal within two to three days. Serum lipase generally reaches its greatest concentration after the amylase value is elevated, but it tends to remain elevated for longer periods. Because of this difference in response, and because the behavior of these enzymes is not always regular, both determinations should be made. The level of serum amylase at a given time in a given patient is governed by a number of factors. As pointed out earlier, normal values may be obtained if the initial determination is made 48 hours or more after the onset of acute pancreatic edema. Occasionally, values below the upper limit of normal may be obtained even in the presence of clinically severe acute necrosis of the pancreas because of extensive destruction of acinar cells. Injection of opiates for relief of pain may result in elevation of both serum amylase and serum lipase for 24 hours, and occasionally for as long as 48 hours.[18] It is well, therefore, to inquire about administration of opiates within the preceding 24 hours when hyperenzymemia is found in a patient with abdominal pain.

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Renal impairment interferes with excretion of amylase. Defective clearance by the kidneys may be responsible for prolonged elevation of amylase in the blood in some cases of acute pancreatitis.[19] Similarly, abnormal serum pancreatic enzyme values may occur in cases of uremia, independent of any pancreatic disease.[20] Other disorders from which primary acute pancreatitis must at times be distinguished may be accompanied by high serum amylase or lipase values without obvious involvement of the pancreas.[20] Such conditions include anterior perforation of duodenal ulcer, intestinal obstruction, and peritonitis. Hyperenzymemia may also occur in hepatic disease.[21] The latter occurrence is of practical importance because of the handicap it places on differential diagnosis when jaundice is also present. Confusion in these several circumstances may be partly avoided if the elevation in serum amylase is great. Values of serum amylase in excess of five times the top normal value indicate primary pancreatitis with rare exceptions.[22] Refinements in the technique used to determine serum enzyme activity may further resolve some of the confusion. Utilization of different substrates, for example, may distinguish the lipolytic activity of pancreatic lipase in human serum from the activity of esterases.[23] Hyperlipasemia [24] and hyperamylasemia [25] may be found in patients with cancer of the pancreas, the former oftener than the latter.[26] Certain limiting factors must be also considered in these cases in interpreting the significance of the serum pancreatic enzyme levels. Chief among these factors are (1) the degree of obstruction of the larger pancreatic ducts, (2) the extent of destruction of acinar tissue, and (3) the stage of the disease at the time the determinations are made. Sizable lesions may exist in the tail, and to a lesser degree in the body of the pancreas, without sufficient obstruction of the larger pancreatic ducts to cause increased diffusion of pancreatic enzymes into the blood. Serum values may be increased early in the disease but may fall in the advanced stages of the disease as more and more enzyme-producing acinar cells become destroyed.[27] Intermittency in values may also be observed; serum enzyme levels may increase at times when a larger duct is occluded and then subside as the acinar cells distal to the point of obstruction cease to function.

The administration of pancreatic secretory stimulants may provoke a rise in serum enzyme values significantly above the fasting or prestimulation levels. Secretin, methacholine (Mecholyl) chloride, bethanechol (Urecholine) chloride, and neostigmine (Prostigmin) methylsulfate have all been used for this purpose. They may be given alone or in various combinations; morphine sulfate may be given in addition to one or more of these stimulants to increase duodenal and sphincteric tone. Provocative elevation of serum enzymes has been observed in some cases of subsiding acute pancreatitis, chronic pancreatitis, and cancer of the pancreas.[28] This method of testing for pancreatic disease has definite limitations, however, that detract from its usefulness.[29] Some observers [29b] have failed to note a consistent difference in the results in control subjects and in patients with pancreatic disease. It is contended that the results do not correlate with the state of pancreatic function as revealed by other means.[29c] Provocative elevation of serum enzymes does not occur regularly in patients with chronic pancreatitis or carcinoma of the pancreas when secretin alone is used as the stimulant,[30] nor can the results be used to differentiate chronic pancreatitis and cancer of the pancreas. Despite these shortcomings, provocative elevation of serum enzymes should arouse suspicion of pancreatic disease. Elevations so produced may supply a clue as to the nature of an earlier-occurring episode of abdominal pain. Furthermore, provocative increase of enzymes in the serum of a patient suspected of having chronic pancreatitis or cancer of the pancreas would lend some support to the clinical suspicion.

Peritoneal Fluid Amylase.—Analysis of peritoneal fluid for amylase content provides another approach to the identification of acute pancreatitis.[31] Material for such analysis may be obtained by aspirating a small amount of fluid from the peritoneal cavity through a 20 gauge needle inserted through the midline of the abdomen just below the umbilicus. Peritoneal fluid amylase values have been reported to remain elevated for from two to four days longer than those of the blood.[31] Values in excess of 300 Somogyi units strongly suggest the presence of acute pancreatitis [32] but should not be considered pathognomonic of this disease; anteriorly perforated duodenal ulcer with escape into the peritoneal cavity of duodenal contents containing pancreatic juices may also result in elevated peritoneal fluid amylase values.[33] Additional examination of the peritoneal fluid for bile and total hydrochloric acid may help to distinguish these conditions.[32]

Urinary Diastase.—Determination of the diastase content of urine provides an easy means of detecting pancreatic disorder, especially with the use of newer and more simplified tests.[34] Opinion varies widely, however, about the value and reliability of such determinations.[19] For the most part, the use of this determination has been limited. Danker and Heifetz [19] point out that urine diastasic activity normally may vary greatly in random specimens of urine. They feel it is wiser, therefore, to express the values as units per hour. They point out, too, that, whereas increased urinary diastase may appear within minutes after blood diastase rises, impaired renal function during acute pancreatitis may delay this appearance. These factors may well explain the variability commonly observed.

Serum Calcium Level.—The serum calcium level tends to be lower when pancreas is acutely inflamed, particularly when the process is severe and attended by fat necrosis. Several mechanisms contribute to the production of hypocalcemia in acute pancreatitis.[35] Probably the most important one is transfer of calcium from the serum to the pancreas and other areas where fat necrosis may have occurred. The calcium drawn to these areas combines with the fatty acids liberated by the hydrolysis of fats to form soaps. The degree of lowering of serum calcium may be used, therefore, as one measure of the severity of the disease. Fall of serum calcium to levels below 7.5 mg. per 100 cc. is a serious omen.[36] Determination of serum calcium also affords information of diagnostic value. Lowered values of serum calcium may become evident at variable intervals after onset of the disease. The lowering, however, does not appear

usually until the second to the fifth day and may persist for two weeks or even longer.[37] When a patient is not seen until a few days after the onset of an acute episode featuring abdominal pain, at which time serum enzyme values may be nonrevealing, the finding of hypocalcemia may serve to identify the process as that of acute pancreatitis.

Serum Alkaline Phosphatase.—Alkaline phosphatase has been shown to be present in the pancreatic juice of man,[38] dog,[39] and rabbit.[38] The enzyme has also been demonstrated by histochemical methods to be present in the intralobular ducts and centroacinar cells of pancreatic tissue of the same species.[38] Elevation of serum alkaline phosphatase has been reported in dogs after pancreatic duct ligation [40] and pancreatitis induced by pancreatic duct ligation and injection of bile from the gallbladder into the ligated duct.[37d] Despite these observations, little attention has been paid to serum alkaline phosphatase as an indicator of pancreatic disease in man.[12b] The investigations of Shay and his co-workers [37d] into the behavior of this enzyme in the blood of dogs with experimentally induced acute pancreatic disease was prompted by a chance observation of persistent hyperphosphatasemia in a patient with acute pancreatitis. Sun,[25f] working in the same laboratory, has noted a significant rise in serum alkaline phosphatase after secretin stimulation in some patients with cancer of the pancreas or chronic pancreatitis. It would seem advisable, therefore, to include this determination among those to be made in evaluating patients suspected of having pancreatic disease. Similarly, elevation of serum alkaline phosphatase in the absence of hyperbilirubinemia should direct attention, among other things, to the possibility of disease of the pancreas.

Alteration in Blood Coagulability.—Relationship between pancreatic disease and alterations in the blood-clotting mechanism has long been suspected.[41] Trypsin has been observed to promote the coagulation of blood.[42] Evidence has also been advanced indicating that trypsin activates a latent lytic substance in the blood.[43] Moreover, hemorrhagic states attributed to excessive proteolytic activity have been noted in patients with cancer of the pancreas.[44] Depending then on the concentration of trypsin in the blood and the net result of the lytic effect of this enzyme on the protein moieties concerned with clotting of blood, coagulation may be increased or decreased. There are no known tests by which level of trypsin in the blood can be reliably measured. In all likelihood, however, the trypsin content of the blood increases and decreases in a fashion parallel to that of the other pancreatic enzymes when pancreatic disease exists. It is possible, however, that the damaged pancreas elaborates some factor other than trypsin that is responsible for the fibrinolytic and thrombinolytic effects observed.[44b]

The antithrombin test is one approach to the diagnosis of pancreatic disease based on alteration in the factors responsible for coagulation of blood.[45] This test purports to measure the antithrombin titer of the blood by determining the clotting time of defibrinated plasma to which standardized thrombin and fibrinogen aliquots are added. Increased plasma antithrombin titers have been observed in cases of acute pancreatitis, in acute exacerbations of chronic relapsing pancreatitis, in cancer of the pancreas with jaundice of less than four weeks' duration, in pancreatic cyst, and in fibrocystic disease in infants.[45] Lowered plasma antithrombin titers have been noted in cases of cancer of the pancreas with jaundice of more than 4 months' duration, in cancer of the pancreas with hepatic metastasis, and in cystic fibrosis of the pancreas with duct obstruction and acinar atrophy.[45] Innerfield and his co-workers [45c] have reported that the plasma antithrombin titer remains elevated throughout the acute phase of pancreatitis. They feel that this is an advantage, since diagnostic plasma antithrombin values may be obtained at stages of acute pancreatitis when serum pancreatic enzyme levels may no longer be increased. Innerfield [45e] has also reported that antithrombin titers may be provocatively increased in cases of chronic relapsing pancreatitis during periods of remission. For this test, a specimen of blood is taken and 1 cc. of 1:2,000 solution of neostigmine is then given subcutaneously; another sample of blood is withdrawn one hour after injection, and the plasma antithrombin titer of this sample is compared with that of the specimen taken immediately before administration of neostigmine. Other observers have confirmed the diagnostic value of antithrombin titer determinations in acute pancreatitis [46] and fibrocystic disease of the pancreas.[47] Not all workers, however, have been successful in the use of this test.[48]

Another approach to the diagnosis of pancreatic disease through detection of an alteration in the coagulability of the blood is the so-called sodium polyanhydromannuronic acid sulfate (Paritol-C) test. This test is founded on three basic premises: 1. Secretory stimulation of a pancreas that is chronically diseased or invaded by carcinoma may result in an increase of blood trypsin. 2. Small increases of trypsin promote the coagulation of blood. 3. Heparin and heparin-like substances such as Paritol-C block the coagulant action of trypsin. A positive result is interpreted as one in which clotting occurs after pancreatic stimulation in tubes containing greater concentrations of polyanhydromannuronic acid than those in which a clot forms before stimulation. Shingleton and others [49] obtained positive results with this test in 6 of 11 patients with cancer of the pancreas and in 6 of 8 patients with chronic pancreatitis. Moser and his associates [50] have recently confirmed these findings.

Stool Changes.—The amount of external pancreatic secretion entering the intestine tends to diminish when the pancreas is diseased. Pancreatic juice may be excluded because of obstruction of the larger pancreatic ducts, and/or insufficient juice may be formed because of destruction of acinar tissue. As pancreatic juice diminishes in quantity and content, digestion of foodstuffs becomes more and more dependent on other enzymes normally present in the stomach and intestine. The capacity for these enzymes to digest fat and protein, particularly the former, is limited. Careful examination of the stools, therefore, may reveal evidence of defective digestion indicative of pancreatic insufficiency. When pancreatic function is significantly impaired and the digestive capacity of the nonpancreatic enzymes is exceeded, the stools become bulky, more numerous, and light-colored.

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The mean weight of the dried feces excreted in 24 hours with the patient on a standard Schmidt diet does not normally exceed 18 gm.; in cases in which pancreatic juice has been largely excluded from the intestine, the weight of the dried stools may be increased to five times or more the average normal amount.[51]

Steatorrhea may be recognized grossly by the light, clay color of the feces, by the presence of butter or cream-like masses on or in the stool,[52] and by a thick, greasy consistency when the stool is smeared. Microscopic examination may reveal droplets or flakes of fat or needle-like crystals.[52] Contrary to previously held opinion, the majority of the fat present will not be of the neutral variety, despite deficiency in pancreatic lipase; apparently, bacteria or other ferments present in the intestine are able to split fat to form fatty acids. An indication of the percentage of fat present in the stool may be obtained through the simple expedient of staining a fecal emulsion with an alcoholic solution of Sudan III. According to Andersen,[53] a negative finding (less than two red or orange-appearing fat droplets per low-power field) and a 4+ finding (half or more of the visible material stained with Sudan) are significant. Accurate determination of the total fat in the feces and of the percentage of fat intake lost in the stool requires a controlled diet of known fat content, collection of stools for a three day period while on this diet, and quantitative analysis of the feces for fat. These pose practical difficulties, which have discouraged general acceptance and use of such analyses. Excretion of fat in the feces in normal persons is usually less than 5% of the fat intake and rarely more than 12 gm. of fat daily.[54] When pancreatic digestion is defective, considerably greater amounts of fat appear in the stool and the percentage of intake excreted in the feces is significantly in excess of normal.

Creatorrhea is perhaps even more indicative of pancreatic insufficiency than is steatorrhea. Impaired protein digestion resulting from pancreatic disease may be recognized by the presence in the feces of a large number of yellow muscle fibers with square ends, sharp edges, and well-preserved striations.[55] A more reliable indicator of pancreatogenous creatorrhea is quantitative measurement of the daily nitrogen excretion in the feces. Daily excretion of more than 3 gm. of nitrogen in the feces may be taken as good evidence of pancreatic disease.[56]

Analysis of the feces may also be used to identify pancreatic insufficiency by estimating the ferment activity of the stool. One such measurement is intended to assay trypsin activity by measuring the proteolytic effect of a fecal emulsion on gelatin. X-ray film is used as the substrate.[57] Impaired digestion of the x-ray film is interpreted to indicate subnormal content of trypsin. Gelatinases, however, may be produced by bacteria present in normal feces and give rise to false results.[57] Johnstone's [57] studies on tests for trypsin in feces indicate that falsely positive tests due to bacterial gelatinases may be reduced by diluting the fecal suspension. The addition of soybean trypsin inhibitor may also serve to distinguish liquefaction due to trypsin from that due to bacterial gelatinase.

Tests for Digestive Efficiency.—The functional capacity of the pancreas may be challenged by giving the patient a test meal requiring pancreatic juice for its digestion. The uptake of the resultant digestive products in the blood, or the amount lost in the feces, is then determined and pancreatic efficiency assayed on the basis of these findings. A gelatin tolerance test was among the first of such procedures to be used. In this test, blood amino acid-nitrogen values are determined before, and at intervals up to four hours after, the ingestion of gelatin. Flat or low blood amino acid-nitrogen curves have been observed in children with cystic fibrosis of the pancreas.[58] Althausen and Uyeyama,[59] however, after using the test in a group of 28 adults with suspected or confirmed pancreatic disease of various types, did not consider it to be a reliable test of pancreatic function in adults. The normality or abnormality of the results depends on the efficiency of intestinal absorption as well as on the degree of protein digestion. This makes it necessary to perform an additional tolerance test using aminoacetic acid in order to rule out impaired intestinal absorption of amino acids when the amino acid-nitrogen curves are low after gelatin.[60] The degrees of protein digestion and absorption may also be measured by giving a test meal of protein labeled with radioactive iodine (I^{131}).[61] Diminished intestinal hydrolysis of protein accompanying deficiency of external pancreatic secretion is evidenced by increased excretion in the feces and decreased excretion in the urine of the administered isotope.

Althausen and Uyeyama [59] have recently devised a starch tolerance test. Blood sugar determinations are made before, and at intervals up to three hours after, the patient has ingested a suspension of starch in water. Since patients with pancreatic disease often have reduced tolerance for glucose, it is necessary also to perform a glucose tolerance test. The extent to which the maximal rise in blood sugar value after administration of glucose exceeds that after administration of starch is calculated in percentages and compared with the established normal range. The outcome of the test was definitely abnormal in 87% of a group of 23 patients with chronic pancreatic disease of different types and in 60% of 10 patients suspected of having chronic pancreatitis.

Examination of Duodenal Contents.—A more direct way of detecting deficient pancreatic secretion, regardless of cause, is by examining the duodenal contents in the fasting state and after pancreatic stimulation.[62] Evidence of pancreatic impairment may be obtained by this method of study before the impairment has progressed to the point of producing changes in the stools.[62d] A double-lumened tube or 2 separate tubes are passed into the stomach and distal part of the duodenum. The contents of the stomach and duodenum are then separately recovered by constant suction. Material is collected for 20 minutes in the fasting state and for from 40 [63] to 80 minutes [62e] after administration of secretin, methacholine, bethanechol, or a combination of secretin and one of the parasympathomimetic drugs. Volume, concentration of bicarbonate, total bicarbonate, and concentration and total output of amylase, lipase, and trypsin are measured in the recovered duodenal contents. As with other tests designed to evaluate pancreatic function by assaying the external secretion of the gland, the secretin test

indicates only that function is intact or impaired; it provides no clue as to the cause for the impairment.

In early stages of pancreatic insufficiency, diminution in enzyme secretion may be the only abnormality.[64] Some investigators feel, however, that if secretin alone is used as the stimulant, determinations of volume and bicarbonate furnish most information regarding the state of external secretion of the pancreas.[65] They believe that enzyme determinations may be omitted without seriously detracting from the value of the secretin test. Since enzyme determinations are tedious and complex, their omission does much to simplify the procedure and make it more adaptable for ordinary clinical use. Secretin given intravenously provokes an outpouring of pancreatic juice into the duodenum. It also stimulates formation of bile,[66] which normally will be stored in the gallbladder. The immediate net result of both of these effects is a diminution in concentration of bile in the duodenal contents. Later, when the flow of pancreatic juice diminishes and the distended gallbladder contracts, bile concentration in the duodenum rises until the situation that existed prior to stimulation is once again restored. Measurement of the icterus index of the duodenal contents, therefore, results in a curve that may provide additional diagnostic information.[67] If the gallbladder has been removed or its storage capacity impaired, the icterus index curve is higher and more sustained than normal. If biliary obstruction is present, the curve is low and flat. The latter finding is especially useful in puzzling cases of jaundice, for it may help to distinguish between a lesion interfering with bile flow alone and one that also affects the pancreatic ducts or the pancreas itself. If, for example, the icterus index curve is flat but the volume, bicarbonate, and enzyme content of the duodenal aspirate are within normal limits, it may be concluded that the obstructing lesion is probably not of pancreatic origin.

Examination of the duodenal contents may provide additional valuable information. Calcium bilirubinate pigment and cholesterol crystals may be evident on microscopic inspection. The finding of these elements points to the existence, alone or concomitantly, of gallstones. Cytological study of the duodenal aspirate is still another diagnostic approach that may provide a clue as to the nature of the underlying lesion. In 16 patients with cancer of the liver, gallbladder, ampullary region, or pancreas, Lemon and Byrnes[68] correctly suspected or diagnosed the disease in 11, on the basis of cytological study of the duodenal aspirations. They and others[69] feel that cytological examination of the sediments of duodenal aspirations is a valuable means of identifying tumors affecting the glandular epithelium of the gallbladder, extrahepatic bile ducts, and pancreas.

ROENTGEN FEATURES

Survey Film of the Chest and Abdomen.—Basal pneumonitis, pleurisy, or even pleural effusion, usually on the left side, may accompany acute pancreatitis.[70] Signs indicative of these changes may be apparent on physical examination, or a roentgenogram of the chest may provide the chief evidence for their existence. Unless one is alert to other features pointing to the pancreas, the secondary supradiaphragmatic change may be mistakenly interpreted as the primary lesion. A plain film of the abdomen often discloses an isolated, gas-filled, "sentinal loop" of small intestine in the middle or upper part of the abdomen of patients with acute pancreatitis.[71] In severe cases, a more diffuse paralytic-type of ileus may be present. Radiopaque gallstones or calcification in the region of the pancreas may also be revealed.

Barium Study of the Gastrointestinal Tract.—Primary pancreatic disorders commonly produce changes in adjacent segments of the gastrointestinal tract through peripancreatic inflammation, cicatrization, pressure, or invasion. The stomach, the pyloroduodenal area, the duodenum, and the transverse colon are most often affected. Which of these areas is altered, and the nature of the alteration, depend on the type of lesion, its size and duration, and its anatomic location in the pancreas. Gastric and duodenal alterations may be observed in patients with acute pancreatitis who are examined soon after acute symptoms have abated.[72] The stomach may be displaced anteriorly, or its silhouette may be altered. The duodenal loop may be widened, the gastric and duodenal mucosa may appear shaggy and edematous, or motility in these segments may be changed. Irregularities in outline and distortion of the mucosal pattern of the stomach or duodenum may be seen in patients with chronic pancreatitis. Cysts of the pancreas characteristically displace the stomach or transverse colon, produce extrinsic pressure defects in the stomach and colon, or widen the duodenal loop.[73] Cancers of the pancreas commonly produce roentgen changes in the mucosal pattern of the pyloroduodenal segment and duodenum[74]; filling defects, depression and widening of the duodenojejunal angle, infiltrative changes, and even ulceration may occur, but widening of the duodenal loop is uncommon.[75] Changes in duodenal motor activity are frequent.[74] Dilatation of the common bile duct causes a pencil-like pressure defect in the immediate postbulbar region and less frequently in the bulb itself.[76] Pressure by the tumor may produce a circumscribed filling defect in the gastric silhouette or the duodenal bulb ("pad" sign).[75b] Tumors in the head of the pancreas may protrude into the inner aspect of the duodenal sweep, immediately above and below the papilla of Vater, producing thereby an appearance described by Frostberg[77] as an inverted "3."

It cannot be overemphasized that barium study of the gastrointestinal tract is one of the most helpful procedures in the study of patients suspected of pancreatic disease. This applies particularly to carcinoma of the pancreas.[78] The importance of careful application and interpretation of this procedure in patients suspected of cancer of the pancreas is illustrated by the experience of Broadbent and Kerman.[78b] Adequate roentgenologic study of the gastrointestinal tract was made in 76 patients with primary carcinoma of the pancreas. When these studies were originally interpreted, carcinoma was definitely suggested in 18% and abnormal changes without a definite diagnosis were noted in an additional 43%. Retrospective review of the same studies led to a definite suggestion of carcinoma in 54% and description of abnormal changes with no definite diagnosis in 25%.

Cholangiography.—Roentgen opacification of the common bile duct may show dilatation of the duct and

interference with emptying of the opaque medium into the duodenum. It may also reveal narrowing of the terminal segment of the duct suggestive of compression or infiltration by a pancreatic lesion. Shehadi [79] succeeded in visualizing a dilated common bile duct by ordinary oral cholecystography in a nonicteric patient with cancer of the head of the pancreas. Such demonstrations may perhaps occur more readily with the use of the newer intravenously administered contrast mediums.[80] Peritoneoscopic cholangiography [81] may be used to opacify the common bile duct in the jaundiced patient in whom neither orally nor intravenously given mediums are effective. This is a procedure whereby contrast material is injected directly into the gallbladder under peritoneoscopic guidance, the ducts becoming opacified secondarily.

Splenoportography.—Inflammatory lesions of the pancreas sometimes extend to affect the portal system of veins, often with resultant thrombosis. Cancers of the pancreas similarly tend to displace and invade these vessels with consequent obstruction of the affected segments. Such alterations may be roentgenologically depicted on films, exposed serially and rapidly, as contrast material is injected directly into the spleen.[82]

Direct Pancreatography.—The pancreatic ducts may be opacified by injecting contrast material through a catheter introduced into the pancreatic ducts at operation.[83] This procedure is still largely in the stage of development. It has some diagnostic promise, however, and has already succeeded in shedding light on the mechanics involved in the production of certain disorders of the pancreas.

GASTROSCOPY

Gastroscopic examination has both negative and positive value in the diagnosis of pancreatic lesions. Its negative value lies in excluding primary lesions of the stomach. From the positive aspect, it may disclose inward bulging of the walls of the stomach caused by an underlying enlarged pancreas.[84]

SUMMARY AND CONCLUSIONS

Clinical, laboratory, and roentgenologic expressions of disorders of the pancreas are numerous, and their diagnostic value is important. Consideration of these features, coupled with heightened awareness of the pancreas, should do much to insure more frequent and earlier recognition of disease of the pancreas.

6767 W. Outer Dr. (35).

ORAL USE OF METHSCOPOLAMINE (PAMINE) BROMIDE IN TREATMENT OF DUODENAL ULCER

EFFECT ON HUMAN GASTRIC SECRETION

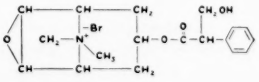
J. Alfred Rider, M.D., Ph.D., John O. Gibbs, M.D., William A. Ranson, M.D.
and
Joyce I. Swader, B.S., San Francisco

"Peptic ulcer is the product of a pathological process as a result of which the gastroduodenal mucosa fails to withstand the digestive action of acid gastric juice." [1] Treatment is limited by the fact that the primary cause of this process is unknown. Nevertheless, free hydrochloric acid seems to be an essential factor in the pathogenesis of peptic ulcer, and satisfactory therapeutic results can be obtained by neutralizing the acid or suppressing its formation. In the past this has been accomplished by the frequent use of antacids, such as calcium carbonate, which chemically neutralize acid. However, since gastric secretion in man is stimulated predominantly via the vagus nerve, there has been an intensive search for drugs that could inhibit vagal impulses either at the parasympathetic ganglions or at the terminal nerve fibers on the parietal cells. Such compounds have been called antisecretory or anticholinergic drugs. Atropine, which has been in use for many years, is the forerunner of this type of therapeutic agent. Whether these agents exert effective ganglionic blocking is controversial, but the main site of action is probably at the nerve endings.

The ideal antisecretory or anticholinergic drug would be one that, administered orally, would consistently produce prolonged inhibtion of acid gastric secretion without the development of tolerance or of undesirable side-effects. It is the purpose of this paper to report the effects of methscopolamine (Pamine) bromide in the treatment of duodenal ulcer and its effect on human gastric acid secretion.

CHEMISTRY AND PHARMACOLOGY

Methscopolamine, the structural formula of which is shown below, differs from atropine in the addition of an



epoxide and a methylbromide group. It is colorless, crystalline, thermostable, and freely water soluble. Visscher and co-workers [2] found that the intravenous injection of methscopolamine had a marked gastric anti-

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2. Visscher, F. E., and others: Pharmacology of Pamine Bromide, J. Pharmacol. & Exper. Therap. **110**: 188-204, 1954.

secretory effect in the "pyloric-ligated rat." Its potency in micrograms per kilogram of body weight was found to be 5 times that of scopolamine hydrobromide, 35 times that of atropine sulfate, and 350 times that of

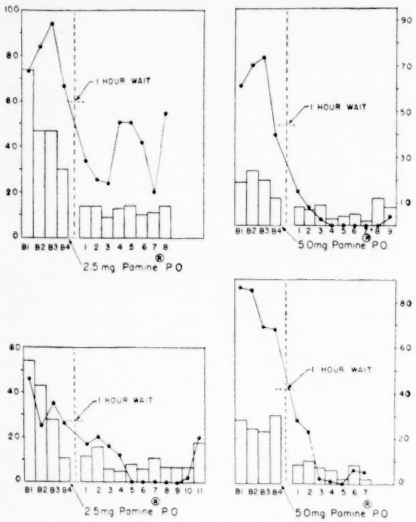

Fig. 1.—Gastric secretory responses of four patients to single orally given test doses of methscopolamine (Pamine) bromide. B1, B2, B3, B4 indicate successive 15-minute collections of basal secretion. In this and subsequent figures, the bars represent volume in milliliters; the line represents free hydrochloric acid in clinical units.

methantheline bromide. Subcutaneous administration to rats of a dose of methscopolamine 2,400 times greater than the effective antisecretory dose given intravenously produced little or no stimulation of the central nervous system. Ganglionic and myoneural blocking actions in animals were manifest only with very high doses. The predominant effects of methscopolamine are: (1) antisecretory on gastric secretion (both volume and free acid), as well as on salivation and perspiration, (2) antispasmodic on the gastrointestinal tract, and (3) mydriatric.

METHODS AND MATERIALS

Study of Effect of the Drug on Human Basal Gastric Secretion.—After the patient had fasted overnight, a Rehfuss tube was passed through his mouth into the stomach. The gastric contents were continuously and completely aspirated by means of a glass syringe, care being taken that the oral secretions were not swallowed. The first aspirate obtained over a two to three minute period was called the residual sample. The next four 15-minute samples were designated basal 1, 2, 3, and 4. The gastric juice obtained during each 15-minute period was measured; free acid was titrated to the salmon pink endpoint of Töpfer's reagent with 0.1 *N* sodium hydroxide. The results obtained were expressed in clinical units. Only patients who had free acid in each of the four 15-minute basal specimens and who had at least 20 clinical units of free hydrochloric acid in one or more of the samples were used in these studies. When these criteria were met, methscopolamine, dissolved in 5 ml. of water, was instilled into the Rehfuss tube, which was then rinsed with an additional 5 ml. of water. After one hour, during which the collection was discontinued, the continuous aspiration was resumed; the secretions obtained during each 15-minute period were tested as before. If anacidity did not occur after at least one hour the test was discontinued. If anacidity did occur, the test was continued until free acid reappeared in the specimens, or as long as practicable.

Study of Clinical Effects in Duodenal Ulcer.—Fifty-five unselected patients with duodenal ulcer were used for clinical testing. The majority had not done well with use of a variety of other medical treatments and

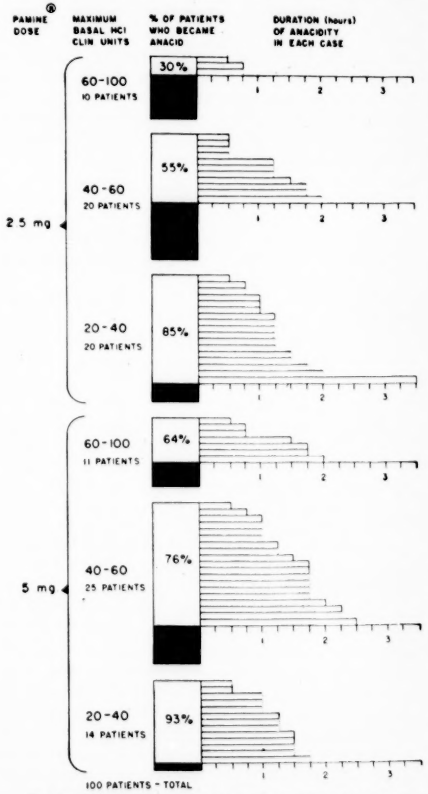

Fig. 2.—Frequency and duration of anacidity after single orally given doses of methscopolamine correlated with the magnitude of the basal hydrochloric acid secretion. The open bars indicate those patients whose gastric secretion was still anacid when the test was discontinued.

could be considered to have "chronic" ulcers. At first, treatment consisted of a diet for patients with ulcers and methscopolamine, given orally in divided doses of from 7.5 to 20 mg. a day, limited only by the severity of un-

pleasant reactions or lack of prompt amelioration of symptoms, in which case antacids were added to the regimen after one to two weeks of therapy.

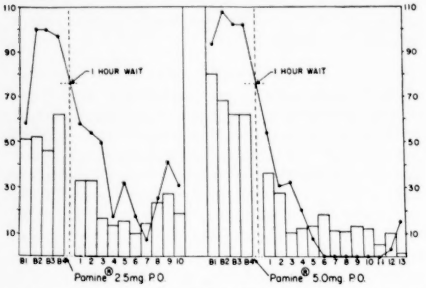

Fig. 3.—Gastric secretory response to single doses of 2.5 and 5 mg. of methscopolamine in the same patients on different days.

RESULTS

Effect on Basal Gastric Secretion.—Typical effects of single orally given doses of 2.5 to 5 mg. of methscopolamine on basal gastric secretion are shown in figure 1. The average effect of methscopolamine on basal gastric secretion in 100 patients is seen in figure 2. It is apparent that the lower the basal acidity and the higher the dose of methscopolamine, the greater the number of patients in whom anacidity was produced. Thus, with a basal acidity of 20 to 40 clinical units and a test dose of 5 mg., the gastric secretions became anacid in 93% of patients, but, with a basal acidity of 60 to 100 clinical units and a dose of 2.5 mg., anacidity developed in only 30%. Side-effects were rarely seen after these single orally given doses. Figure 2 also shows duration of anacidity after administration of methscopolamine in each patient. Since some of the tests were discontinued before free acid returned, it was not possible to obtain an average value for the duration of anacidity. The maximum period of anacidity observed was three and one-half hours. No attempt was made to calculate the individual degree of reduction in free acidity in those patients in whom anacidity was not produced. Even though it was observed that in the great majority of these patients acidity was decreased after methscopolamine, we evaluated individually only those to whom we could apply the more precise criterion of anacidity.

Average Values for Volume and Free Hydrochloric Acid in Basal Samples and in Hour of Response to Single Orally Given Doses of Methscopolamine

	50 Patients Given 2.5 Mg. Dose		50 Patients Given 5 Mg. Dose	
	Volume, Ml.	Hydrochloric Acid, Free Clinical Units	Volume, Ml.	Hydrochloric Acid, Free Clinical Units
Average 4 basal samples	24.0	35	31.3	39.3
Average 4 samples in hour of methscopolamine response	12.2	11.6	13.7	7.3
% decrease	49.3	67.2	56.3	81.5

The table shows the average volume and average acidity of the four basal samples of 50 patients who were tested with 2.5 mg. of methscopolamine and 50 patients who were tested with 5 mg. The basal values are compared with the results obtained after the single dose of methscopolamine. It can be seen that the 5 mg. dose is the more effective since there was a decrease of 81.5% in the free acidity, but the decrease in volume was not significantly greater. Similar results were obtained when a repeat gastric analysis after a single orally given dose of 2.5 mg. of methscopolamine was compared to a gastric analysis after a 5 mg. dose in the same patient. Figure 3 shows the gastric secretory response to single doses of 2.5 and 5 mg. of methscopolamine in a representative patient. The results indicate that in the same patient the larger dose is more effective.

To determine whether prolonged therapy with methscopolamine would influence the acidity and volume of the basal gastric secretion, repeat gastric analyses were done on 25 patients who were maintained on a schedule of 7.5 to 40 mg. of methscopolamine a day in divided doses for periods up to 18 months. Figure 4*A* compares the average basal gastric acidity and volume before therapy with that during prolonged therapy. It can be seen that the residual samples showed no decrease in volume but that free acidity was reduced by 34.3%. The four basal samples showed a fall in volume of 28.8% and a decrease in free hydrochloric acid of 30.6%. In 10 of these patients, gastric analyses after single doses of methscopolamine were repeated on numerous occasions during maintenance on daily doses of methscopolamine. Figure 4*B* compares the average

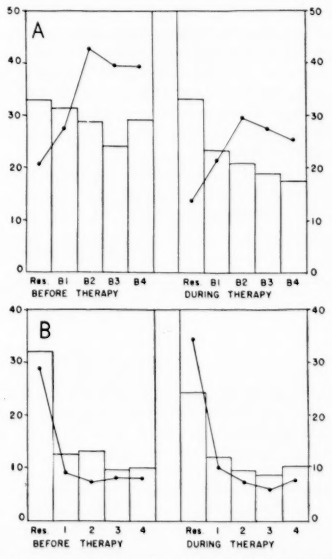

Fig. 4.—*A*, basal gastric secretion before and during methscopolamine therapy, averages of 25 patients. *B*, gastric secretory response to single orally given test doses of methscopolamine before and during therapy, averages of 10 patients.

volume and free acid of the gastric secretions of these patients after the first test dose of methscopolamine with those of subsequent tests (with the same dose) during daily maintenance therapy with methscopolamine. These results indicate that the inhibitory effect of methscopolamine on gastric secretions does not decrease, even during prolonged therapy, nor does it increase.

Clinical Results in Treatment of Duodenal Ulcer.—Fifty-five patients with "chronic" ulcer were first treated with methscopolamine and diet alone. The dose of methscopolamine was frequently, but not always, increased to the point of unpleasant side-effects; yet only 7.3% of the patients became symptom-free with doses of from 7.5 to 40 mg. of methscopolamine a day. The usual dose schedule was 2.5 mg. before meals and 5 mg. at bedtime. When it became apparent that methscopolamine and diet alone were not completely effective in the majority of these patients, antacids were added as indicated, but in no case was it necessary for the patient to take antacids during the night. The usual antacid was calcium carbonate or an aluminum hydroxide preparation. The therapeutic results in the 55 patients treated for periods up to 18 months were as follows. In 36.4% of these patients it was necessary to use antacids from one to four times per day. In 56.3% administration of antacids was necessary every two hours during the day. Of the total group treated, 63.7% were completely asymptomatic and 30.8% had occasional symptoms; only 5.4% continued to have fairly regular symptoms, but these seemed easier to control than before treatment. It can be seen that the majority became asymptomatic as a result of combined treatment with methscopolamine and minimal to moderate amounts of antacids. X-ray evidence of healing closely paralleled sustained relief of symptoms.

The severity, type, and frequency of undesirable side-effects in these patients were as follows. There were 51 instances of side-effects in 33 patients. Dryness of the mouth was present in 20, constipation in 18, blurring of vision in 9, and difficult micturition in 4. Forty per cent of the patients manifested no side-effects. Even though some undesirable reactions occurred in the majority of patients, in only one were they severe enough to require discontinuing treatment.

SUMMARY AND CONCLUSIONS

Methscopolamine (Pamine) bromide is an orally effective parasympatholytic drug that blocks vagal impulses to the parietal cells at the terminal fibers or at the cellular level. It inhibits gastric secretion by decreasing both volume and free hydrochloric acid. Study of the effect of single orally given doses of methscopolamine on the basal secretory pattern shows that the higher the initial level of free hydrochloric acid, the larger the dose of methscopolamine required to induce anacidity. Repeated basal gastric analyses during prolonged therapy with methscopolamine demonstrated decreases in both volume and free acidity compared to the pretreatment levels. No diminution in the effect of single tests doses of methscopolamine on gastric secretion was observed after prolonged daily administration of the drug.

Undesirable reactions occurred in 60% of 55 patients with duodenal ulcer receiving an average daily dose of 12.5 mg. These were usually mild and only rarely prevented continued administration of the drug. Methscopolamine alone rarely produced complete relief of symptoms; clinical results were much more satisfactory when antacids were added to the therapeutic regimen. Although methscopolamine is not a substitute for conventional ulcer management, it is a valuable adjunct and makes management of the patient easier. We agree with Kirsner, Levin, and Palmer [3] that the ideal gastric antisecretory agent has not been found but that substantial progress has been made toward this objective.

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END-RESULT OBSERVATIONS INFLUENCING TREATMENT OF FRACTURES OF THE SHAFT OF THE TIBIA

Marshall R. Urist, M.D., Los Angeles

Fractures of the leg, especially comminuted fractures of the tibia and fibula, heal more slowly and present more complications than those of almost any other skeletal area. At the level of middle and lower thirds, the tibia is composed chiefly of dense compact bone, a lining of inactive substantia spongiosa, and a medullary cavity filled with fatty bone marrow. The periosteum in this location has hardly any capacity for proliferation of external callus. The fracture must heal mainly by means of endosteal new bone formation. The process is extremely slow and the period of healing is necessarily prolonged under these circumstances, especially if bone contact is slight or if there is actual separation of the fracture surfaces.[1] Surgical treatment fails to alter the indolence of the tibia. The tibia justifies Pease's [2] criticism of modern fracture treatment more than any other part of the skeleton; it gives little support to those who may take the affirmative in the current debate about open versus closed treatment.[3]

In a recent paper, I, with Mazet and McLean,[4] reported the results of a study of matched cases among 100 consecutive healed fractures and 85 ununited fractures of the tibia. In this study the emphasis was on the pathogenesis and treatment of delayed union and nonunion, and these subjects were given detailed consideration. The present paper makes use of the same material, but with a different purpose in mind. The effort here has been to draw conclusions from the end-results of the

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fractures studied that bear on the choice and course of treatment from the time of the injury. The objective, of course, is to select methods of treatment that will lead to the most favorable results possible, and that will avoid the complications of sepsis, slow healing, and nonunion. The material studied is rich in contributions to this objective.

The results of this study lead inevitably to the general statement that closed treatment of fractures of the tibia is superior in every way, and under nearly all circumstances, to open reduction. This conclusion is reached in spite of the increasing use of open methods of surgery; the considerations entering into the conclusion are examined below.

CLOSED TREATMENT

Long-term end-result survey reports of the past 20 years have established the conclusion that closed treatment of fractures of the tibia, in skilled hands, is superior in every respect to open reduction.[5] Such treatment presupposes a well-fitted properly padded long leg cast with appropriate after-care. The criteria for this judgment include: (1) diminution in the period of hospitalization; (2) reduction in the costs of medical care; and (3) reduction in the over-all risks of complications, including sepsis and delayed healing or nonunion. The evidence in favor of closed methods of treatment is especially compelling in cases of fresh comminuted fractures of the tibia. These fractures have always been the most difficult problem with respect to the shaft of the tibia.[6] The end-results show without doubt that closed treatment is the only safe procedure and that such fractures should, in fact, be regarded as nonoperable, in the sense that open operation is almost certain to be detrimental to the welfare of the patient.

The skill required for closed treatment seems not to be valued highly enough by the laity or by the medical profession at the present time. The result is that closed treatment, in the case of the lower leg, at least, is not as generally used as it should be. The effort, patience, and time required to treat a fracture of the tibia and fibula by closed methods for nine months are fully as great as by open methods. It is unfortunate that not all surgeons are able to develop the required skills with closed methods, or to achieve consistently good results with conservative treatment. Charnley's reiteration of the principles and practice of closed treatment of fractures and his technique of holding the reduction by internal angulation of the fracture should be reviewed by those who are dissatisfied with nonoperative methods.[5c] In addition to his technical skill in the management of fractures by closed methods, the surgeon must be prepared to instruct the patient in the special problems of the tibia and to explain why it is in his best interest that he should tolerate a cast for a longer time than he had expected. The surgeon may anticipate that the patient will tell him about a friend who had an open operation and was out of plaster several months earlier, but he will often have heard of another patient who had an infection and nonunion or amputation following an open operation. It is then not difficult to convince him that conservative treatment is indicated.

Disadvantages of Closed Treatment.—The disadvantages of closed treatment include the considerations that lead so frequently to open treatment. The skin becomes mummified after long periods of encasement in plaster. The joints tend to become stiffened. The bones develop the atrophy of disuse. Causalgia, intractable edema and swelling, and decubitus ulcers unfortunately do occur in many cases. It does not follow, however, that these complications are preventable by current methods of open treatment, even though these methods may reduce the time the leg is in plaster.

Contraindications to the Use of Internal Fixation.—The surgeon may be aided in his decision to adopt conservative methods of treatment of fractures of the tibia by a consideration of the contraindications to the use of alternative methods. In view of favorable results following internal fixation in fractures of the femur, it has been perhaps inevitable that this should become a popular method also of treatment of fractures of the tibia, a bone that lends itself equally well to the mechanical aspects of this procedure. A large enough number of poor results and complications have, however, accumulated to diminish the use of this method, in fractures of the tibia, in the majority of teaching centers in the United States. It is difficult to determine whether these more conservative policies have or will have any effect on the over-all practice of fracture surgery in the community. For the resident in training the picture is especially confused by the conflicting factors of (1) the justifiable use of transfixation screws without bone plates for certain spiral fractures, and (2) extravagant claims for the new designs of devices for intramedullary fixation for the tibia.

The type of fracture that responds well to open surgery is precisely that which gives good results also by closed methods. Transfixation screws, bone plates, Parham bands, and intramedullary nails are generally successful in noncomminuted fractures, but these may be treated at least equally well without open operation. The chief beneficial effect of open reduction is to eliminate separation of the fracture surfaces, and thereby to reduce healing time. This can reduce the time in plaster as much as two or three months. Against this possibility, however, must be weighed the added risks of sepsis and of delayed healing or nonunion introduced by open reduction

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6. Parson, L.: Fractures of the Shaft of the Long Bones of the Leg, in Experience in the Management of Fractures and Dislocations, edited by P. D. Wilson, Philadelphia, J. B. Lippincott Company, 1938.

and internal fixation. The evidence against the choice of open operation in fresh comminuted fractures of the tibia is overwhelming. Surgical intervention in such fractures is seldom, if ever, justifiable.

The series reported by me with Mazet and McLean was studied by matching cases of closed fracture with those treated by all forms of internal fixation, including transfixation pins. Internal fixation never decreased and often actually prolonged the healing time. Necrosis and absorption of bone occurred between the screws, especially if they were placed too close together (less than 1 cm. apart). This retarded healing and, sometimes but not always, led to nonunion. Interrupted immobilization, ill-advised early weight-bearing, and friction and motion between bone ends were some of the critical factors leading to nonunion following open treatment.

Sepsis.—Even in this era of the everyday use of antibiotic drugs for the prevention and treatment of infection, approximately 7% of compound comminuted fractures of the tibia are complicated by sepsis. The incidence of secondary osteomyelitis is increased to 12% when fractures originally closed but treated by open operation are added to this group of wound infections. Except in instances in which internal fixation was applied per primam intentionem, it can be assumed that sepsis was unavoidable. At least 3% of the cases in any random series of compound fractures seem to have been contaminated with foreign material and bacteria against which injured tissues have only an inadequate defense. Primary treatment for compound fractures that has proved by experience to be quite satisfactory is as follows: (1) a bold incision with minimum or no dissection of the bone ends; (2) thorough irrigation of the wound with at least 2,000 cc. of isotonic sodium chloride solution; (3) excision of all tissue that appears to be contused, macerated, or necrotic; (4) manipulation and reduction without internal fixation; (5) loose closure of the wound if the operation was performed less than 8 to 16 hours after injury; (6) a properly-padded well-fitted long leg plaster encasement; and (7) daily injections of 400,000 I. U. of penicillin, accompanied by 1.0 gm. per day of streptomycin by mouth.

It is reasonable to assume that in the hands of a surgeon with a great deal of experience with compound comminuted fractures, the incidence of wound infection may be reduced from 7 to 2 or 3% by the use of the above outlined treatment. In cases in which there had been an open operation with internal fixation, the infection is much more extensive, prolonged, and resistant to treatment than in cases in which there had been no metallic fixation. The saddest picture of all is the x-ray film that shows a perfect piece of cabinet work with a bone plate in a leg that had to be amputated because of overwhelming sepsis. There were three such instances in patients admitted to the Wadsworth service from outlying hospitals from 1948 to 1953.[4]

Infected compound fractures wisely treated without metallic implants rarely develop chronic osteomyelitis or require amputation. The infection is often limited to a very small area of the bone or involves only soft parts on the medial aspect of the leg. Prolonged immobilization in plaster is the best treatment after the necessary local management of the wound, such as with wet dressings, sodium hypochlorite (Dakin's solution), or newer enzyme preparations to dissolve slough. It is generally believed that after six months without drainage it is safe to attempt a surgical attack on the fracture site to improve the position of the fracture or to apply internal fixation or a bone graft. End-result observations show that this generalization is false. After a fracture of the tibia has been infected, there is no safe period for open operation. The best indications are the condition of the skin and the appearance of the bone ends in the roentgenograms. Edematous skin and scars with bluish discoloration adherent to the scar suggest conditions adverse for surgery. A diffuse osteoplastic reaction in one or the other of the bone ends indicates latent infection that might flare up after surgical incision of the fracture and the overlying tissues.

AIDS TO CLOSED TREATMENT

Comminuted fractures, especially the oblique types with single wedge-shaped fragments, are sometimes difficult to retain in good position in a plaster cast alone. Some contact between the bone ends is absolutely essential if union is to be expected within a year. The greater the surface area and the closer the contact, the less the healing time. It must be emphasized, however, that restoration of alignment, as can be seen in the gross appearance of a straight leg, is required for satisfactory treatment of a severely comminuted fracture. When the fragments are not in contact, or when the leg is grossly shortened (more than 1.0 cm.) and deformed by the forces of muscle contraction, there are three methods that are used as aids to closed treatment. These methods were employed in the cases I observed as follows:

Skeletal Traction.—Compound comminuted fractures with loss of skin and bone substance and with sepsis were managed in skeletal traction with a 5 lb. (2.3 kg.) weight to prevent gross angulation or bowing. The method has the advantage of being a great convenience for dressing of large wounds and for watching the circulation of a severely damaged wound. For this reason, it was advocated by the surgeon general for treatment of shell-fragment fractures in World War II. The correct use of the method depends upon transfer of the limb to a long leg plaster within four to six weeks. For longer periods, it does not give enough immobilization to restrict motion and friction and to prevent delayed healing or nonunion. It is not usually advised for noncomminuted fractures of the shaft of the tibia or any type that can be treated successfully in any other way.[5a]

Transfixation Pins in Plaster.—Application of transfixation pins in plaster is often used for unstable fractures to avoid the hazards of open reduction and internal fixation. The pins become bent inside the plaster to bring the fracture ends together whenever great distraction is applied to hold the reduction. When one considers the extraordinary tension produced in leg-lengthening operations, there is some reason to doubt that the idea of distraction, a major cause of delayed union, deserves the emphasis it has been given in the literature. It is clear, however, that the healing time is proportional to the amount of separation of the bone fragments and length of the damaged portion of the shaft. Comminuted frac-

tures with single wedge fragments account for most of the "unstable fractures" classified as delayed union. This type may require as long as 9 months to heal and could unite if treated by transfixation for only 6 weeks and then left undisturbed in plaster for 12 to 18 months. It should be noted, however, that transfixation pins to prevent overriding were often unnecessary if the leg was immobilized with the knee at 100 degrees flexion in the first plaster, and 160 degrees in the second plaster. Furthermore, it is advisable to allow a certain amount of shortening—up to 1.0 cm.—to allow the fragments of a comminuted fracture to come together to obtain earlier union. This is preferable to forceful methods of retaining the original length of the leg. Slow healing or delayed union were described in approximately 10% of comminuted fractures treated with pins through plaster. Pin tract infections and skin slough also occur but can be regarded as results of errors in technique.

External Skeletal Fixation.—The Haines, Roger-Anderson, and Stader apparatus can be found covered with the dust of 10 years' time in splint rooms in nearly all large medical centers. Occasionally one or the other of these splints has been brought out and applied in some one case or special research problem. But even for limited purposes their use has been short-lived. The reason has not been so much because of pin tract infections, delayed union, and other complications but actually because closed methods in plaster are more comfortable for the patient and achieve the same or better end-results. The situation is much the same as in the history of many clinical research projects. The individual who introduces a new method gives it so much care and attention and achieves such proficiency that the results are less dependent upon the method than upon the diligence and good judgment with which it was applied.

OPEN SURGICAL TREATMENT

Open treatment of the tibia ordinarily consists of surgical exposure of the fracture site and direct manipulation of the bone ends until the fracture surfaces are brought in close contact. The procedure is rarely finished without application of some form of fixation to maintain the reduction. But the wise surgeon omits this step when dealing with compound or any other kind of fractures in very young children. He simply holds the fracture together manually until the wound is closed and the leg is immobilized in plaster. Even in adults, this is not done often enough. The temptation to make an extensive dissection to apply rigid internal fixation is too much to resist for the inexperienced or mechanically minded surgeon. It must be admitted, however, that technical skill can overcome many of the objections to open surgical treatment. Internal fixation can be applied without complete dissection of soft parts from the bone ends. An expert surgeon can exhibit excellent results from internal fixation in a large number of cases.

Modern history records many attempts to devise a set of rules for the use of internal fixation by the many surgeons who profess to treat fractures. Thus far all such attempts to establish a universal standard or policy have failed to have any appreciable influence on the over-all conduct of fracture treatment. Actually, it is impossible to treat a consecutive series of fractures of the tibia by open methods without doing unnecessary surgery on at least half of the patients. This is the basic reason for failure of the strong proponents of open reduction and internal fixation of the past. The majority of its proponents today practice the principle that a surgeon's armamentarium must include a knowledge of the use of all methods and appliances. Inasmuch as it is the end-result, not the method of achieving it, that is most important, the knowledge of what not to do to the human tibia is the heart of the problem of treatment of fractures of the leg.

There are at least five different types of internal fixation that a surgeon should know he must not use routinely for the treatment of some fractures of the shaft of the tibia. The indications and frequency of the use of each differs now from when it was first introduced and, in some instances, even from the way it was used only 10 years ago. The passage of time, hospital teaching policies, and influential authoritative writers have affected the general picture of treatment of the tibia in many ways. At the present time there appears to be more uncertainty and controversy than ever before—perhaps because there is now a larger number of methods. The conclusions gained from the Wadsworth series [4] about the value, contraindications, and current usage of each method will be summarized briefly below.

Transfixation Screw.—The transfixation screw was employed only for long, oblique, or spiral fractures. It was frequently successful when the operative technique was correct and one screw was all that was needed to hold the fracture together long enough to sew up the wound and apply a close-fitting, very slightly padded, long leg cast. If two screws were used and placed at least 2 or 3 cm. apart for a long spiral fracture, a good result and union was usually obtained within six months. More than one or two screws usually hindered rather than helped bone repair. If the screws were placed less than 1 cm. apart at any one point, necrosis and disintegration of bone occurred between them. Another error in technique in the use of transfixation screws and the main predisposing factor in delayed healing and nonunion was excessive stripping of soft parts from the fracture fragments to apply internal fixation. The overall incidence of delayed union with this method was not less than 7%.[7]

Bone Plates.—Lane plates were used with success in noncomminuted transverse or short oblique fractures but frequently caused disaster in comminuted fractures. Sepsis, infection, and large skin slough were the usual complications. Newer designs of sliding bone plates were not more effective than nonsliding plates. The effect on the course of fracture healing appeared to be the same as with Lane plates. Bone plates were rarely used by surgeons with a great deal of experience with other methods of treatment of fractures of the tibia. Bone plates were, however, readily available on the shelves of the surgical stock rooms of all small and large hospitals

7. White, E. H.; Radley, T. J., and Earley, N. N.: Screw Stabilization in Fractures of Tibial Shaft, J. Bone & Joint Surg. **35A**: 749-755, 1953.

and used by physicians and surgeons of all specialties on all types of fractures. The over-all incidence of delayed healing and nonunion was more than 30%.

Parham Bands.—Parham bands are not generally available in all hospitals. This appliance was used by a few individuals who were highly experienced and well-informed about its limitations. One surgeon who specialized in ski accidents treated long spiral fractures of the tibia with success by this method. Parham bands for fractures in general have been discarded nearly everywhere in the United States.

Wire (Cerclage).—The technique of using wire consists of application of a loop of wire across one or two sides of the cortex to tie the bone ends together in order to prevent gross displacement from occurring inside the cast. The method has been popular in France and in a few localities in America. In general, it is not held in very high regard. It has been used most effectively after débridement of compound fractures in which larger metal appliances would not be well tolerated. It was useful in noncomminuted transverse and short oblique fractures but hardly worth the effort for comminuted fractures. The wire broke very soon after patients were allowed up in walking plasters if the fracture was not completely consolidated.

Intramedullary Fixation.—The intramedullary nail has not occupied the same important place in the treatment of fractures of the tibia as in the femur. European investigators very early found that the tibia was not as receptive as other parts of the skeleton, which proliferate and heal readily following a fracture. New designs of the intramedullary nail with a special curve at the distal end are now available for the specific purpose of rigid internal fixation of fractures of the tibia. Many successful results have been reported with a relatively low percentage of delayed healing or nonunion. The situation with respect to this new method, however, is that it appears to be most successful in noncomminuted fractures, which ordinarily heal well within six months by conservative treatment in plaster. It is dangerous, as are other open methods in the compound comminuted fractures, which are the main problem of treatment of the tibia. In fractures at the junction of the middle and lower thirds, which heal very slowly, the nail does not give particularly good fixation of a short distal fragment. Unless the fracture is in the middle or upper third, and the nail fits very tightly, it has been hardly possible to dispense with a long leg cast. After all of these considerations are carefully weighed against the risks of open surgery, it is very difficult to find a case in which intramedullary nailing of the tibia is really indicated. The possibilities of intramedullary nailing techniques that do not open the main fracture site, however, do offer interesting fields for further investigation.

DELAYED HEALING AND NONUNION

Many clinical causes and combinations of causes such as (1) separation of bone surfaces, (2) exposed bone, (3) sepsis, (4) excessive internal fixation, and (5) insufficient immobilization appear to be responsible for delayed healing and nonunion. The permutations and combinations of these factors are enormous, so that it is usually impossible to be certain that any one cause is the true cause of nonunion.[8] Whatever the clinical circumstances may be, there appears to be one and only one mechanism of nonunion. Newer histochemical techniques applied to the study of biopsy specimens of fractures have revealed fibrinoid degeneration of connective tissue in the interior of the callus in all patients with delayed healing and nonunion, regardless of the clinical cause that led to the complication.[4] Morphologically, fibrinoid is a mixture of collagen and ground-substance in all stages of degradation. As the term suggests, it is like fibrin, but it is not fibrin. This material accumulates in the callus whenever there is extensive necrosis of tissue, sepsis, and insufficient immobilization of the fracture. Motion and friction stimulate the production of fibrinoid. The process appears to be similar to that seen in chronic adventitious bursitis except that fibrinoid is deposited inside of a mass of inflammatory connective tissue between the bone ends rather than over a bony prominence. Microscopically, fibrinoid appears in the callus as an acellular, homogeneous, highly refractile, acidophilic material. Its mucopolysaccharide component stains metachromatically with toluidine blue or a pink color with the McManus-Hotchkiss procedure. Fibrinoid appears as a mixture of colors with Mallory's stain. X-ray diffraction and electron-microscope studies reveal disoriented collagen fibers in the early stages and chiefly amorphous material in the later stages of fibrinoid degeneration.

The formation of a pseudarthrosis develops after a single or repeated mechanical disturbance has split the amorphous fibrinoid material into two parts. Fibrinoid imbibes water and forms a cavity filled with mucinous fluid in the center of the callus. Hydrostatic pressure created by osmosis may reach such proportions as to break metallic appliances used for internal fixation and to refracture surrounding areas of bone. With continued motion and friction between the fracture surfaces, new bone formation occurs all around but not across the main fragments. The bone ends show rounding, mushrooming, and molding of the opposing surfaces. The bone tissue becomes sclerotic, and the medullary canal becomes sealed with compact bone. The appearance of the x-ray picture gives the impression that bone repair is at a standstill. In many cases this is an erroneous idea and not the true state of affairs, especially if the observation is less that 18 months after injury. Formation and resorption of bone are endlessly active processes everywhere in the skeleton, including the area of a fracture. For this reason there are many cases, even at this late stage, that will unite if the fracture is immobilized for a longer period of time in plaster, or by means of a synostosis operation that does not include the fracture site.

Immobilization of the fracture prevents further motion, friction, and mechanical inflammation and stops further formation of fibrinoid in the callus. The defects refill with granulation tissue, fibrous tissue, and fibro-

8. Watson-Jones, R., and Coltart, W. D.: Slow Union of Fractures, with Study of 804 Fractures of Shafts of Tibia and Femur, Brit. J. Surg. **30**: 260-276, 1943. Watson-Jones, R.: Fractures and Joint Injuries, Baltimore, Williams & Wilkins Company, 1946, vol. 1.

cartilage, which are then replaced by new bone. The same effect can be elicited by a bone graft operation. An onlay bone graft implanted across the surface of the fracture without excision of fibrocartilaginous callus seems to introduce two factors: (1) an internal splint and (2) a new proliferative response and new bone formation by induction across the fracture gap. Autogenous, homogenous, heterogenous, and even boiled bone has been found to produce union of the fracture. The success of the operation depends primarily upon the condition of the bone ends and the proliferative response of the bone tissue near the fracture; only secondarily does it depend upon the bone grafting material or the mechanics of the surgical technique. The role of the bone graft is that of an inductor. Its effect is like that of a catalyst in a chemical process, since it does not itself enter into the reaction between the bone ends but induces it by a physical-chemical effect that occurs as soon as contact is established between the donor tissue and the host bed.[9]

COMMENT

Resident training institutions and specialty examining boards emphasize the principle that there is wisdom and virtue in treating fractures of the tibia like those of any other long bone; that is, first by closed methods and efficient immobilization and then by surgery only if other methods fail. In actual practice in the community, however, open treatment of the tibia without any attempt to use closed methods is far commoner than is necessary or desirable for the welfare of the patient. This difference between academic teaching and actual practice on patients is the heart of the "fracture problem."

The practice of fracture surgery by physicians at large in the community is influenced by psychological, social, and economic factors, which are many and complex. It is not within the scope of this communication to discuss economic pressures that confront the doctor and that confuse the patient in many instances. Only one fact observed by me and my associates needs special emphasis. Nonoperative methods of management of the tibia require as much or more professional background, ability, effort, and patience than open reduction or internal fixation operations. A surgeon's competence with the tibia should, thus, be judged chiefly by his ability to perform closed operations.

This report is written in an effort to clarify the situation with respect to indications and contraindications for open and closed treatment of fractures of the tibia. It does not, as other recent communications have done,[10] attempt a broader consideration of the use of open and closed methods, nor is it intended to depreciate open treatment of fractures of other areas, e. g., the neck of the femur, the patella, the head of the radius, and other fractures inside of joints. The conclusions arrived at in this report lead to the belief that the surgeon should be encouraged to use closed methods oftener in treatment of fractures of the tibia, because this policy can diminish: (1) the period of hospitalization; (2) the costs of medical care; (3) the over-all risks of complications; and (4) the incidence of delayed healing and nonunion.

SUMMARY AND CONCLUSIONS

Fractures of the shaft of the tibia present special problems to the surgeon, requiring attention to considerations not necessarily present in fractures of other bones. Closed treatment of fractures of the tibia is superior in every way, and under nearly all circumstances, to open reduction and internal fixation. Fresh comminuted fractures of the tibia should be regarded as nonoperable, in the sense that open surgical treatment is almost certain to be detrimental to the welfare of the patient. The mechanism of delayed healing and nonunion of fractures, whatever may be the clinical causes and combination of causes, appears always to be the occurrence of fibrinoid degeneration of connective tissue in the interior of the callus. New methods of attack on the problem of the slow-healing tibia should be evaluated in comparison with nonoperative treatment, rather than with other operative methods of management. Since nonoperative methods of treatment of fractures of the tibia require as much or more professional ability, effort, and patience than open reduction and internal fixation, the skill needed for closed treatment should be held in higher regard than it is now by the medical profession and by the laity.

1019 Gayley Ave. (24).

9. Urist, M. R., and McLean, F. C.: Symposium on Skeletal Trauma: The Local Physiology of Bone Repair with Particular Reference to the Process of New Bone Formation by Induction, Am. J. Surg. **85**: 444-448, 1953. Urist, M. R.: The Physiologic Basis of Bone Graft Surgery with Special Reference to the Process of New Bone Formation by Induction, in Clinical Orthopaedics, edited by A. F. DePalma, Philadelphia, J. B. Lippincott Company, 1953, vol. 1, pp. 207-216. Urist, Mazet, and McLean.[4]

10. Jaslow.[2] Pease.[2]

The Sodium in Water.—With the exception of occasional casual mention, drinking water has been overlooked as a source of sodium sufficiently large to nullify attempts to restrict that element in the rest of the diet. The determination of the Na content of the water supply should be an essential part of the establishment of a restricted sodium regimen. Where the upper NaCl limit prescribed is low, such as the Kempner rice diet for hypertensive patients, even a very low concentration in the water supply may be very significant. In such cases, it is very likely that a de-ionized or distilled water may be required, for even the usually low-sodium surface supplies may prove objectionable. . . . Of paramount importance is recognition of the potential problem by the attending physician and the dietitian on the case, in order that the efficacy of otherwise carefully planned diets and conscientious application by the patient may not be contravened. The additional effort involved in analyzing the situation is certainly justified, even though it may be significant and applicable for only a small minority of all cases in which this type of therapy is indicated. Recognition is significant also from the standpoint of certain complications that occasionally accompany sodium restriction therapy, notably the "sodium depletion" syndrome. To date, relatively few complications have been reported, possibly because the rigidity of sodium restriction frequently is not as great as that prescribed. With increasingly more complete information now at hand for the physician and dietitian pertaining to sources and actual amounts of sodium taken into the body, the degree of sodium restriction may be increased and perhaps more frequent complications will be realized unless otherwise compensated for.—E. J. Laubusch and C. S. McCammon, M.D., Water as a Sodium Source and Its Relation to Sodium Restriction Therapy, *American Journal of Public Health*, October, 1955.

CLINICAL EXPERIENCE WITH WARFARIN (COUMADIN) SODIUM, A NEW ANTICOAGULANT

Col. Byron E. Pollock (MC), U. S. Army

Although the presently available anticoagulants have been of great clinical usefulness, well-recognized defects are inherent in them. Heparin requires frequent parenteral administration and is costly. Bishydroxycoumarin (Dicumarol) has a long latent period between the time of administration and onset of therapeutic effect. Ethyl biscoumacetate (Tromexan) loses therapeutic effect within a few hours after reaching the therapeutic level, thus rendering smooth control of anticoagulant action difficult. Other of the newer anticoagulants possess undesirable side-reactions. A more nearly ideal anticoagulant continues to be a practical need. For this reason a clinical study has been conducted on warfarin (Coumadin) sodium, one of the group of coumarin drugs produced by Dr. Karl Paul Link and his group at the University of Wisconsin.[1] The substance, 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin, is highly active as a hypoprothrombinemic agent, is soluble and stable, and is suitable for intravenous use. The relationship of warfarin sodium to bishydroxycoumarin is shown in fig. 1.

Animal experiments in Professor Link's laboratory [2] have shown this substance to possess no effects other than hemorrhage at excessive dosage and to produce a much greater hypoprothrombinemic effect weight for weight than bishydroxycoumarin. This effect is reversible with menadione and phytonadione (vitamin K_1). Lange and Terveer [3] in 1954 added information on toxicity of this substance to the human in their report of accidental warfarin poisoning in a family of 14 Korean civilians who ingested over a 15 day period 50 lb. (23 kg.) of mixed corn meal rodenticide containing 5.8 gm. of warfarin. In spite of excessive amounts as compared to clinical dosage, it was 7 days before symptoms appeared, 15 days before a death occurred, and the 12 patients who received treatment recovered.

From the Cardiology Service, Fitzsimons Army Hospital, Denver.

Read before the first annual meeting of the American College of Angiology, Atlantic City, N. J., June 4, 1955.

The warfarin sodium used in this study was supplied as Coumadin sodium by Dr. Samuel M. Gordon, Endo Products, Inc., Richmond Hill, N. Y.

1. Ikawa, M.; Stahmann, M. A., and Link, K. P.: Studies on 4-Hydroxycoumarins: V. The Condensation of Alpha, Beta-Unsaturated Ketones with 4-Hydroxycoumarin, J. Am. Chem. Soc. **66**: 902-906 (June) 1944. Overman, R. S., and others: Studies on the Hemorrhagic Sweet Clover Disease: XIII. Anticoagulant Activity and Structure in the 4-Hydroxycoumarin Group, J. Biol. Chem. **153**: 5-24 (April) 1944. Seidman, M.; Robertson, D. N., and Link, K. P.: Studies on 4-Hydroxycoumarins: X. Acylation of 3-(α-Phenyl-β-Acetylethyl)-4-Hydroxycoumarin, J. Am. Chem. Soc. **72**: 5193-5195 (Nov.) 1950.

2. Shapiro, S.: (*a*) Warfarin Sodium Derivative (Coumadin Sodium): An Intravenous Hypoprothrombinemia-Inducing Agent, Angiology **4**: 380-390 (Aug.) 1953; (*b*) The Hypoprothrombinemia-Inducing Activity of Warfarin Sodium (Coumadin Sodium), J. Kansas M. Soc. **55**: 687-691 (Dec.) 1954.

3. Lange, P. F., and Terveer, J.: Warfarin Poisoning: Report of 14 Cases, U. S. Armed Forces M. J. **5**: 872-877 (June) 1954.

4. Wolff, J. M.; Barker, N. W.; Gifford, R. W., and Mann, F. D.: Experience with a New Intravenous Coumarin Anticoagulant (Warfarin, Sodium Derivative), Proc. Staff Meet., Mayo Clin. **28**: 489-497 (Sept. 9) 1953.

5. Clatanoff, D. V.; Triggs, P. O., and Meyer, O. O.: Clinical Experience with Coumarin Anticoagulants Warfarin and Warfarin Sodium, A. M. A. Arch. Int. Med. **94**: 213-220 (Aug.) 1954.

6. Quick, A. J.: The Clinical Application of the Hippuric Acid and the Prothrombin Tests, Am. J. Clin. Path. **10**: 222-233 (March) 1940.

Earlier reports on clinical experience with the intravenous administration of the drug were made in 1953 by Shapiro,[2a] who used warfarin sodium in 100 cases, and by Wolff and associates,[4] who gave 35 injections of warfarin sodium in the treatment of 29 patients. Clatanoff and his associates [5] reported in 1954 the effect of intravenously administered warfarin sodium in 20 patients and of orally administered warfarin or warfarin sodium in 16 patients.

METHOD

My use of warfarin sodium given intravenously as an anticoagulant was begun in May, 1953, and, in March, 1954, I began use of tablets for oral administration. Ten cubic centimeter ampuls of warfarin sodium containing 75 mg. of the drug were secured for intravenous use. Scored tablets prepared in 25 mg. size were used for oral administration.

Patients with acute thrombophebitis, pulmonary embolism, myocardial infarction, or other conditions requiring anticoagulant therapy were given initial dosage of 50 to 80 mg. of the drug either orally or intravenously after determination of prothrombin time was accomplished. Prothrombin determinations were made daily at 8 a. m. thereafter and the required maintenance dose of the drug estimated. With few exceptions, attempts were made to achieve constant levels within the therapeutic range by daily dosage with warfarin sodium after the peak effect of the initial dose had been reached. Prothrombin tests were performed on 100% plasma by the one-stage method of Quick [6] with use of thromboplastin (Simplastin), and results were reported both as prothrombin time in seconds and as a percentage of normal prothrombin. Control prothrombin times were usually 13 seconds and rarely 12 or 14, which were considered 100% of normal. Whenever hypoprothrombinemia became excessive or hemorrhage of gross or microscopic proportions occurred, menadione sodium bisulfite or phytonadione (Mephyton) was administered parenterally in a single dose.

RESULTS

I have treated 100 patients with warfarin sodium as shown in table 1. All of the patients were adults; age varied from 21 to 91 years. The series includes 42 cases of myocardial infarction, 12 cases of intermediate coronary syndrome (coronary insufficiency), 35 cases of acute thrombophlebitis, 7 cases of pulmonary embolism, 2 cases of congestive heart failure, and 2 cases of chronic auricular fibrillation preparatory to conversion to normal rhythm.

Initial Dosage.—The 21 patients given initial dosage of the drug by the intravenous route received a total of 23 injections (2 patients had two courses of anticoagulant therapy). Initial administration of 75 mg. proved adequate to produce therapeutic hypoprothrombinemia in 15 cases (83%) and was insufficient in 3 instances.

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In one patient an 80 mg. initial dose was effective. An initial dose of 50 mg. given in four cases proved insufficient in three. Warfarin sodium was given orally as the initial dose 81 times in 79 patients. A dose of 75 mg.

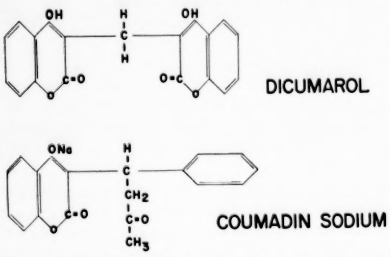

Fig. 1.—Structural relationship of warfarin (Coumadin) sodium to bishydroxycoumarin (Dicumarol).

proved adequate in 47 instances, was insufficient for optimal effect 15 times, and was excessive in 5 cases. A dose of 87.5 mg. was adequate the one time it was

Method of Administration of Warfarin (Coumadin) Sodium

Initial Dose	Maintenance	No. of Cases
Intravenous	Intravenous	13
Intravenous	Oral	8
Oral	Oral	79
		100

used. An initial dose of 50 mg. proved inadequate seven times, adequate five times, and excessive once. No direct correlation between body weight and size of initial dose was found.

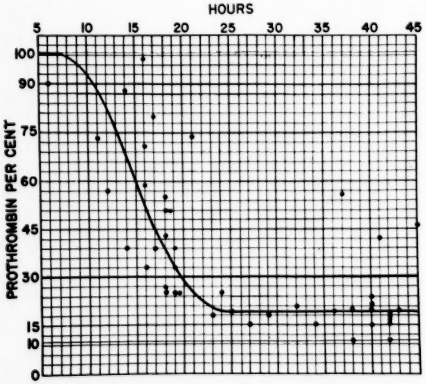

Fig. 2.—Hypoprothrombinemic effect of 75 mg. of warfarin sodium given intravenously in 18 cases.

Reduction in prothrombin levels to clinical anticoagulant effect (10 to 30% of normal) followed intravenous administration of the drug by an average of 21 hours and oral administration by an average of 24 hours (fig. 2 and 3). Somewhat greater variability is seen in response to oral medication, but, on the average, the effect of the same initial dose given orally instead of intravenously is to delay the response approximately three hours and to reach final levels of prothrombin percentage about 5% higher (25% of normal instead of 20% of normal) (fig. 4).

Duration of effect of a single (initial) dose could not often be determined from our records because of the interference of maintenance doses given before the full effect of the initial administration of the drug had been expended. Our records do show examples, however, of duration of therapeutic prothrombin levels for six days in 4 instances and for three to five days in 18 further cases (fig. 5).

Maintenance Dosage.—The average maintenance dose of warfarin sodium varied from 4 mg. to 19 mg. per day in individual cases, whether given intravenously or orally. The average maintenance dose for all patients was about 10 mg. per day (9.85 mg. for patients given

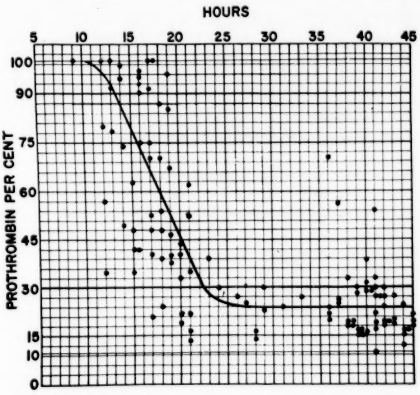

Fig. 3.—Hypoprothrombinemic effect of 75 mg. of warfarin sodium given orally in 60 cases.

maintenance therapy intravenously and 9.74 mg. per day for patients maintained with tablets for oral use). Again there was no direct correlation with the patients' weight, but the daily maintenance dosage in any one individual remained remarkably constant (fig. 6). Return of prothrombin time to normal (13 or 14 seconds) could be followed in 46 instances and occurred from one to three days (average two days) after the time of the last determination found within therapeutic range.

Hemorrhage and Hypoprothrobinemia.—Evidence of gross or microscopic bleeding was encountered in eight cases. In three of these a hypoprothrombinemic cause appears remote. One individual subject to epistaxis experienced a brief period of minor bleeding from the nose while his prothrombin level was at 13% of normal. The bleeding stopped spontaneously without alteration of anticoagulant therapy and did not recur. A second patient treated for thrombophlebitis soon after a prostatectomy was performed suffered from some bleeding into the bladder while the prothrombin level was 16% of

normal; bleeding stopped after evacuation of the clots and without use of vitamin K derivatives. In the third patient in this group petechiae formed over an area of swelling in the leg due to thrombophlebitis. The prothrombin level was at 19% of normal on this, the second day of anticoagulant therapy. Treatment was not altered, and no further hemorrhagic manifestations occurred.

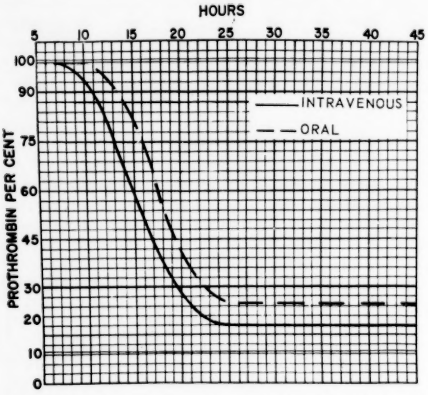

Fig. 4.—Comparison of hypoprothrombinemic action of single dose of warfarin sodium given intravenously and orally.

Hematuria occurred six times in five patients. In one case microscopic hematuria was noted on the 11th day of intravenous therapy with warfarin, with the prothrombin level at 18% of normal. The patient was given 50 mg. of phytonadione intravenously, with recovery in one day and elevation of prothrombin to 68%. In a second case microscopic hematuria appeared at a prothrombin level of 10.5% and cleared without the administration of vitamin K. In three cases (four episodes) excessive hypoprothrombinemia under oral therapy was present with prothrombin levels below 10% when gross hematuria occurred (prothrombin times were 47 seconds, 48 seconds, 44 seconds, and 44 seconds respectively). Intravenous administration of phytonadione in dosage of 10, 10, 5, and 5 mg. reduced prothrombin time to 15, 14, 14, and 13 seconds, respectively, by the following morning; this represents prothrombin percentages varying from 50 to 100%; hematuria disappeared.

Either vitamin K or phytonadione was used in five instances in which bleeding did not occur. In two of these menadione sodium bisulfite in 36 and 72 mg. doses given intramuscularly was used to counteract hypoprothrombinemia (7% and 9% of normal respectively); by the following morning prothrombin levels showed good return toward normal (16 and 56%). In one case phytonadione was administered when a rough pericardial friction rub developed in a patient with myocardial infarction. Phytonadione, 50 mg. introduced intravenously, elevated prothrombin from 13% to 100% of normal by the following morning. In two instances phytonadione was given to restore prothrombin levels in preparation for surgery. A 50 mg. dose given intravenously increased the prothrombin level from 22 and 17% to 100 and 53%, respectively, within 17 hours. Frequent prothrombin determinations were not made after the administration of the vitamin K products, so that the exact time of onset of their action was not delineated.

Hypoprothrombinemia (levels below 10% of normal) occurred 15 times in 10 cases without hemorrhage, and recovery to therapeutic levels was allowed to proceed spontaneously by withholding maintenance medication. These periods were of one day's duration or less in 11 instances, two days in 2 instances, and three days in 2 instances. Prothrombin times varied from 38.7 seconds to 75 seconds.

Clinical Data.—A total of 20,518 mg. of warfarin sodium was given to 100 patients over an average period of 15.8 days for an average daily dosage of 13 mg. and a total of 1,579 patient days of accumulated experience. No effect of warfarin sodium was seen during this study other than the production of hypoprothrombinemia. Four deaths occurred during treatment of this series of patients. Three were due to myocardial infarction: one through rupture of the heart, one in general collapse with gradual cessation of cardiac action, and one through apparent ventricular fibrillation. One death was due to rupture of a cerebral vessel. It does not appear that the anticoagulant therapy contributed to these deaths. In the remainder of cases anticoagulant action of the drug accomplished the desired therapeutic action well, with the development of no complications other than the cases of minor bleeding cited above. Pulmonary

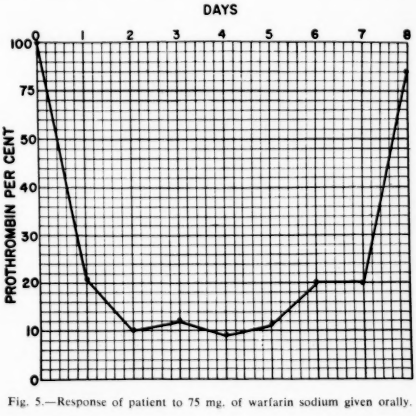

Fig. 5.—Response of patient to 75 mg. of warfarin sodium given orally.

embolization was not observed in any of these patients while they were undergoing therapeutic hypoprothrombinemia.

COMMENT

Warfarin sodium is a rapidly acting anticoagulant drug producing therapeutic hypoprothrombinemia in approximately 21 hours when administered intravenously and 24 hours when administered orally. Absorption must be almost complete from the intestinal canal, since the

response to doses given orally and intravenously is approximately the same, with a delay of about three hours in the onset and peak of action when the drug is given orally. Heparin may be used during induction of therapeutic hypoprothrombinemia, as was done in 28 cases, provided care is taken that blood for prothrombin determination is not drawn within four hours of the administration of heparin. Rarely will it be necessary to use heparin therapy for more than 24 hours when warfarin is administered as the primary anticoagulant.

Maintenance of smooth levels of hypoprothrombinemia proved to be relatively easy due to the prolonged action of the drug. In instances where the initial dosage of 75 mg. of warfarin sodium proved inadequate, supplementary dosage corrected the defect without difficulty. Administration of phytonadione restored prothrombin to safe levels and led to clinical cessation of bleeding in all instances in which it was attributable to

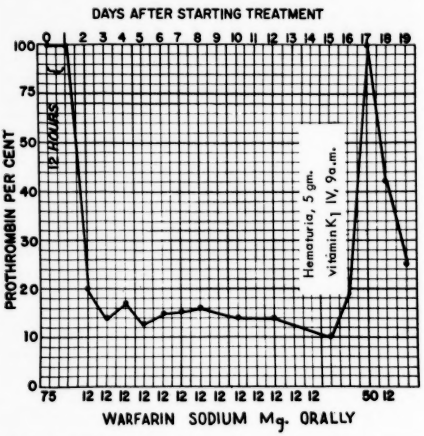

Fig. 6.—Prothrombin response to small dose of phytonadione (vitamin K_1).

hypoprothrombinemia. In this connection it was noted that small intravenously given doses of phytonadione (5 to 10 mg.) were effective in raising prothrombin levels and did not produce the resistance to further anticoagulant therapy commonly noted with larger doses (25 to 50 mg.). Individual variability of response to warfarin sodium, as with other anticoagulants, renders frequent determinations of prothrombin necessary. Although occasional levels of hypoprothrombinemia below 10% of normal may be tolerated, excessively low levels or long continuation of levels below 10% of normal lead to bleeding, manifested by microscopic or gross hematuria and perhaps other manifestations.

My experience with warfarin sodium is parallel in most respects to that of Shapiro [3a] with regard to the intravenous use of the drug and with that of Clatanoff and his associates [5] in the use of the form for oral use. In my experience, warfarin sodium possesses properties that more nearly approach the ideal anticoagulant than the other drugs currently available: early anticoagulant effect, smoothness of maintenance, lack of side-reactions, and ease of restoration of prothrombin with phytonadione. The advantage of an agent that may be given either orally or intravenously depending upon the clinical situation is obvious.

SUMMARY

Warfarin (Coumadin) sodium, a 4-hydroxycoumarin drug, has been used as the hypoprothrombinemia agent in 100 clinical cases requiring anticoagulant therapy. This substance is soluble and active by intravenous and oral administration in approximately the same dosage. The initial dose was given intravenously in 21 cases, orally in 79. Maintenance dosage was given intravenously in 13 of the former group and orally in the remaining 87 cases. Therapeutic hypoprothrombinemia is induced in adults by an initial dose of approximately 75 mg. of the drug within an average of 21 to 24 hours, depending upon the route of administration. The maintenance dose by the continuous method, based on frequent (daily) prothrombin determinations, varied among patients from 4 to 19 mg., averaging about 10 mg. whether the drug was given orally or intravenously, and was consistent from day to day in the same patient. Prothrombin returned to normal levels after therapy with warfarin sodium was discontinued in an average of two days measured from the time of the last determination within therapeutic levels.

Hemorrhagic phenomena occurred in eight cases and were attributable to anticoagulant therapy in five of these cases (5%). They consisted of gross or microscopic hematuria, which cleared rapidly on administration of phytonadione. Menadione sodium bisulfite or phytonadione was administered in 10 instances for various reasons and invariably produced significant elevation of the prothrombin level. No side-effects (effects other than the induction of hypoprothrombinemia) were encountered. None of the four deaths that occurred in patients of the series were attributable to anticoagulant therapy; clinical estimate of the results of anticoagulant therapy was uniformly good. It is concluded that warfarin sodium possesses properties that make it more nearly an ideal anticoagulant than the other agents now available.

Cortisone in Treatment of Infectious Hepatitis.—Cortisone in both the oral and parenteral form appears of definite value in the treatment of hepatitis because: 1. It caused a more rapid clearing of jaundice, as measured by the average icterus index and serum bilirubin levels, than occurred in the controls. 2. It caused a more rapid return of the appetite than occurred in the controls. 3. It caused the patients treated with it to consume more food than did the controls. 4. It caused a greater gain in weight than occurred in the controls. 5. The bromsulphalein tests in the cortisone-treated patients on the average returned to normal faster than they did in the controls. 6. The patients treated with cortisone got well faster than did the controls. Because of these six findings we feel that cortisone is of definite value in the treatment of hepatitis. We do not recommend the use of so potent a drug as routine therapy for hepatitis, but we feel that it should be of great value in those cases of hepatitis which do not respond to conventional treatment.—Lieut. Col. T. E. Huber and Capt. A. T. Wiley, (MC), U. S. Army: Cortisone in the Treatment of Infectious Hepatitis, *Annals of Internal Medicine*, May, 1955.

STUDIES WITH GLUCAGON IN PATIENTS WITH INSULIN SENSITIVITY

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and
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The regulatory mechanisms that come into play in response to a sharp decline of the blood sugar concentration, restoring its equilibrium (hypoglycemia responsiveness), and the impairment of these mechanisms in spontaneous hypoglycemia or induced hypoglycemia (hypoglycemia unresponsiveness) are not clearly understood. However, it has been established that the responsiveness of certain organs or systems seems to be of primary importance in such homeostasis. These are (1) the sympathico-medullo-adrenal system, (2) the anterior pituitary and the adrenal cortex, and (3) the glycogenolytic responsiveness of the liver.

Hypoglycemia responsiveness has been investigated in man and experimental animal, by studying insulin sensitivity, in the sense of measuring the rate of decline of the glucose content in the blood after a given test dose of insulin. A number of methods have been designed for the study of the kinetics of blood sugar elimination from the blood stream, and modifications of these have appeared in the literature during recent years. The "assimilation index," which was introduced as early as 1929 by Norgaard and Thaysen,[1] was calculated from the decline of the blood sugar level during an insulin tolerance test. Himsworth [2] devised the glucose-insulin tolerance test, which he applied in classifying diabetic patients into insulin-sensitive and insulin-insensitive. In 1941, Fraser, Albright, and Smith [3] used three types of tolerance tests for the study of impaired carbohydrate metabolism in endocrinopathies, and a modified test was described later by Engel and Scott [4] for the detection of hypoglycemia unresponsiveness in pituitary and adrenal insufficiency. By applying modified techniques there has been an attempt to give a mathematical expression to the rate of fall of the glucose concentration in the blood stream, and such figures are given in expressing the rate of decline, or the disappearance rate of glucose, or the glucose assimilation coefficient.[5] All these tests study the decline phase of the tolerance curves and they are, with certain limitations, of diagnostic value, but they do not furnish any further information concerning which of the homeostatic mechanisms mentioned may be impaired.

Glucagon, the hyperglycemic factor of the pancreas has been shown from in vivo and in vitro experiments to produce hyperglycemia by stimulating selectively hepatic glycogenolysis. The promptness of this effect and its failure to produce any side-effects make it a valuable tool for the study of certain aspects of hypoglycemia responsiveness. Pincus [6] found an increased hyperglycemic response to glucagon in patients with unstable diabetes, but a decreased response was obtained in similar patients by Kirtley and others.[7] Their conflicting results could be explained by the different "basal conditions" used and the different preparations administered. Kibler and Myers [8] have used the responsiveness to glucagon as a test of liver function; they found a better correlation of this method in severe liver disease as compared to the liver function tests usually applied. Hubble [9] and others have found no response to glucagon in patients with von Gierke's disease. The present study was undertaken to explore further the possibility of applying glucagon as a diagnostic tool in patients with insulin sensitivity and to accumulate information about the importance of hepatic glycogen reserves in the regulatory homeostatic mechanisms during hypoglycemia.

MATERIAL AND METHODS

Nine adult subjects of both sexes were selected as normal controls: two were normal individuals and seven were hospitalized orthopedic patients. These patients were in the latter part of the third postoperative week recovering from intervertebral disk surgery. They were all in good health, none were diabetic as judged by normal postprandial blood sugar, and all were well nourished on a high-caloric, high-carbohydrate diet. In a few cases a high-carbohydrate preparatory diet, as recommended by Conn,[10] was introduced three days prior to the experiment. If any drugs were being used they were withdrawn 24 hours prior to the experiment.

Fifteen adult diabetic patients of both sexes (more than 25 years of age) were divided into two groups: six patients with stable diabetes and nine patients with "brittle" diabetes, according to a classification that is based on a percentage expression of the blood sugar values for each patient. This classification has been presented in another study.[11] Patients with stable diabetes were selected as controls for patients with brittle diabetes. All diabetic patients studied had been followed for a number of years at the department of endocrinology at the Cleveland Clinic and were under treatment with insulin and controlled diet. All six patients with stable diabetes were under good control. The nine patients with brittle diabetes showed the usual fluctuations in their blood sugar values. Attempts were made to obtain a normal fasting blood sugar value by observing these patients a number of days prior to the experiment and modifying their insulin requirements accordingly. Experiments were not done in patients who had had an insulin reaction during the previous 24 hours.

A few patients with miscellaneous conditions, presenting hypoglycemia unresponsiveness, diagnosed clinically and on the basis of repeated low blood sugar values,

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The glucagon used in this study was supplied by Dr. W. R. Kirtley and Eli Lilly & Company, Indianapolis.

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were studied. Four patients with adrenal cortical hypofunction (Addison's disease) were included in this group. The diagnosis in each case was based on the classical history and the physical and the laboratory findings. The experiments on patients with adrenal cortical hypofunction were performed three days after withdrawal of steroid treatment, and the only therapy given was sodium chloride. During this period the patients were on a high-caloric, high-carbohydrate diet and their weight was maintained. One patient with an islet cell tumor was studied preoperatively. The diagnosis in this case was confirmed at surgery.

Two patients with functional hypoglycemia were studied. For three days preceding the experiments these individuals were given a high-carbohydrate preparatory diet. Two patients with total pancreatectomy and one with subtotal pancreatectomy (two-thirds resection)

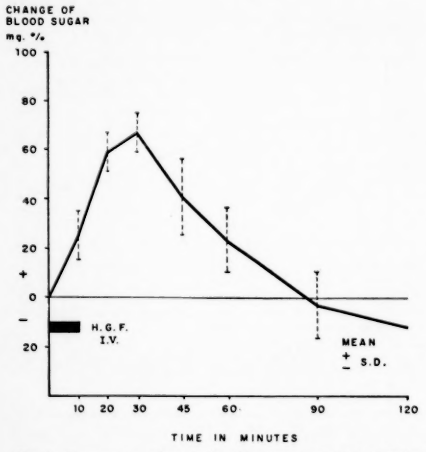

Fig. 1.—Response to glucagon in nine normal controls. H.G.F.= glucagon.

performed for cancer of the pancreas were investigated. These patients showed blood sugar fluctuations similar to those seen in patients with brittle diabetes and occasionally had insulin reactions. At the time of the experiments they had no diarrhea, maintained their weight, the liver was not palpable, and there was no clinical evidence of metastasis. One diabetic patient with hemochromatosis also was investigated.

Most patients were admitted to the hospital for these studies for a period of five to seven days, while a few were ambulatory except for the days of the experiment. On day 1, diabetic patients received their usual morning dose of insulin with which they had been controlled. No insulin was administered after that time, and no food was given after 6 p. m. of that day. On day 2, no food was given and diabetic patients received no insulin. The nonhospitalized patients were permitted to rest for a two hour period prior to the experiment. All experiments were performed at rest 16 to 17 hours postprandially and were started between 10 and 11 a. m. of day 2. At zero time (day 2), venous blood was withdrawn and immediately after 0.6 mg. of glucagon was administered intravenously in 50 cc. of isotonic sodium chloride solution within 10 minutes. The same dose was used in all experiments. Venous blood was withdrawn at 10 minute

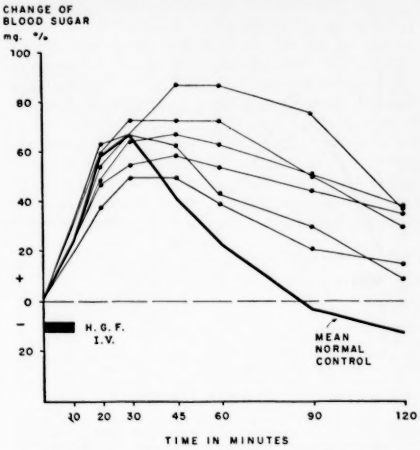

Fig. 2.—Response to glucagon in six patients with stable diabetes.

intervals for the first half hour, every 15 minutes the second half hour, and in half-hour intervals for the next hour. At the end of two hours the experiment was terminated and the patients received their noon meals; their diabetes was controlled with two doses of regular insulin for the rest of the day. Day 3 was a rest period.

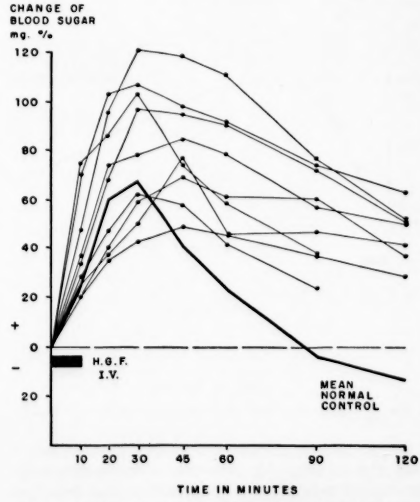

Fig. 3.—Response to glucagon in nine patients with "brittle" diabetes.

Diabetic patients received their usual diet and morning dose of insulin as on day 1. On day 4, the same procedure was repeated on the same patient with the addition of 15 units of regular insulin given subcutaneously three hours (at 7 or 8 a. m.) prior to the infusion of

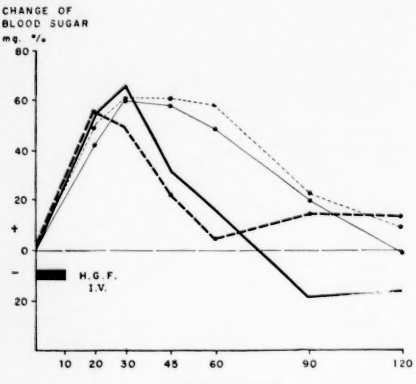

Fig. 4.—Response to glucagon in two normal controls. The two upper curves are from one patient (before glucagon indicated by solid light line, and after glucagon indicated by broken light line). The two lower curves are from the second patient (before glucagon indicated by solid heavy line, and after glucagon indicated by broken heavy line).

glucagon. The same period of fasting was used as in day 2 in each experiment. In a small number of the normal controls and Addisonian patients, three hours prior to the second glucagon test, 25 mg. of corticotropin (ACTH) intramuscularly was administered.

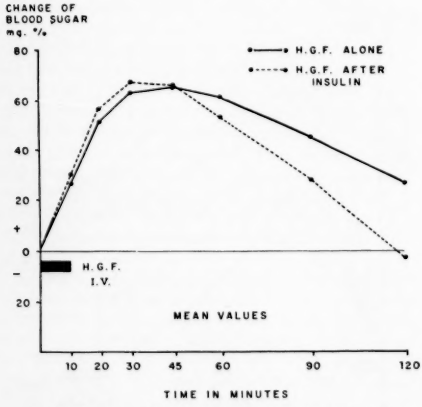

Fig. 5.—Response to glucagon in six patients with stable diabetes.

In two patients with adrenal cortical hypofunction a third glucagon test was performed a few months after the original experiments. These studies were done two hours after 50 mg. of hydrocortisone had been administered by mouth. Blood specimens were analyzed for glucose by the method of Somogyi and Nelson.[12] Total blood ketone bodies and, in a small number of studies, ultracentrifugal patterns of lipoproteins were determined.

RESULTS

Figure 1 demonstrates the mean blood sugar curve (± standard deviation [S. D.]) obtained in response to an intravenous injection of glucagon in nine normal controls. The maximum rise was obtained in 30 minutes after the start of the infusion. The mean maximum increase above the initial zero value was 66.4 mg. per 100 cc. (S. D. ±7.9). At the end of 90 minutes blood sugar values had returned to normal or slightly below normal. No subject in this group experienced any hypoglycemic reaction during the second hour after the infusion.

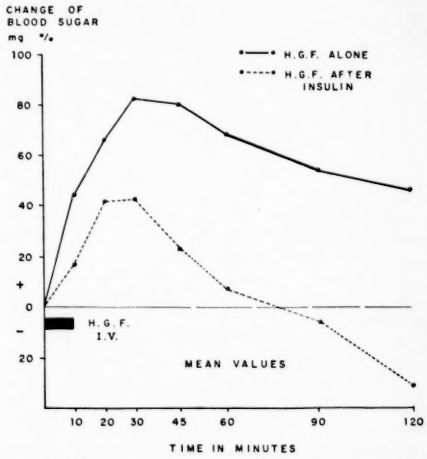

Fig. 6.—Response to glucagon in nine patients with brittle diabetes.

Figure 2 records the hyperglycemic responses of six patients with stable diabetes. The darker line indicates the mean value in normal controls. The mean response was 62.5 mg. per 100 cc. in 30 minutes and the mean maximum response 65.2 mg. per 100 cc. in 45 minutes. One patient in this group gave a maximum response of 87 mg. per 100 cc. at 45 and 60 minutes, but that of all others fell in the range of the maximum response of normal controls. In all six patients differences occurred in the specimens taken at 60, 90, and 120 minutes as compared to the normal controls. At the end of two hours all patients with stable diabetes had blood sugar values above control level.

Figure 3 shows the response curves obtained in nine patients with brittle diabetes. The mean maximum response was 82.1 mg. per 100 cc. in 30 minutes. Two patients showed maximum response in 45 minutes. All patients with brittle diabetes, with one exception, gave hyperglycemic responses above the mean of normal controls and patients with stable diabetes. Some patients

with brittle diabetes gave a hyperglycemic response in the range from 97 to 121 mg. per 100 cc. No relationship was observed between the level of the zero time blood sugar value and the magnitude of the hyperglycemic response. Figures 4, 5, and 6 record the hyperglycemic responses to glucagon when given alone, as compared to the responses when glucagon was given three hours after the administration of 15 units of regular insulin intramuscularly. In figure 4 the findings in two normal subjects are presented, and in figure 5 the mean values of six patients with stable diabetes are plotted. In normal controls and in patients with stable diabetes the hyperglycemic effect of glucagon was essentially the same when given alone or when given after insulin. Figure 6 shows the results of the same experiment in patients with brittle diabetes. In the latter the difference between the two responses is marked. In table 1 the glycemic reactions after 90 or 120 minutes. In three normal controls the differences of responses were compared when glucagon was administered alone and when it was given three hours after a single dose of 25 mg. of corticotropin intramuscularly. In these experiments one normal subject showed an increase of 31 mg. per 100 cc. in 30 minutes above the response obtained when glucagon was given alone and 38 mg. per 100 cc. in 45 minutes. The other two normal subjects gave essentially the same changes with and without corticotropin. No significant differences in the hyperglycemic response were obtained in two patients with adrenal cortical hypofunction when glucagon was given alone and when it was given three hours after a single dose of 25 mg. of corticotropin or two hours after 50 mg. of hydrocortisone by mouth. In all cases after the administration of corticotropin or hydrocortisone, the zero time values

TABLE 1.—*Change in Blood Sugar Level in Response to Glucagon in Patients with Stable and Brittle Diabetes*

	Time, Min.																					
	10			20			30			45			60			90			120		
Patient	A*	I†	A-I‡	A	I	A-I	A	I	A-I	A	I	A-I	A	I	A-I	A	I	A-I	A	I	A-I
Stable																					
1.....	....	+31	....	+54	+69	+15	+66	+65	− 1	+63	+48	−15	+43	+36	− 7	+30	+19	−11	+ 9	....	....
2.....	+24	+25	+ 1	+49	+56	+ 7	+64	+61	− 3	+68	+62	− 6	+63	....	....	+51	+25	−26	+30	....	....
3.....	....	....	....	+38	+44	+ 6	+50	+59	+ 9	+49	+51	+ 2	+39	+38	− 1	+21	+21	0	+15	+ 9	− 6
4.....	....	....	....	+48	+41	− 7	+55	+56	+ 1	+59	+67	+ 8	....	+38	....	....	+ 1	....	+35	−22	−57
5.....	....	....	....	+59	+61	+ 2	+73	+89	+ 7	....	+82	....	+73	+61	−12	+50	+48	− 2	+39	+35	− 4
6.....	....	....	....	+63	+68	+ 5	+67	+85	+18	+87	+88	+ 1	+87	+82	− 5	+76	+59	−17	+37	+15	−22
Brittle																					
1.....	....	....	....	+41	+37	− 4	+59	+32	−27	+69	+21	−48	+61	+ 1	−60	+61	−19	−80	+37	−41	−78
2.....	....	+28	....	+68	+31	−37	+97	+52	−45	+95	+29	−66	+90	+27	−63	+72	+ 8	−64	+62	....	....
3.....	+25	+18	− 7	+47	....	....	+62	+21	−41	+58	+ 6	−52	+42	−15	−57	+24	−44	−68	....	....	....
4.....	+26	+15	−11	+37	+30	− 7	+50	+21	−29	+77	+12	−65	+46	− 3	−49	+47	−29	−76	+42	−40	−82
5.....	+20	+ 1.5	−18.5	+35	+28	− 7	+43	+33	−10	+49	+ 6	−43	+46	....	....	+37	−24	−61	+29	−36	−65
6.....	....	....	....	+74	+44	−30	+97	+31	−66	+85	+ 3	−82	+79	−13	−92	+57	−21	−78	+46	−22	−68
7.....	+70	+25	−45	+103	+47	−56	+107	+52	−55	+98	+34	−64	+92	+22	−70	+74	+ 2	−72	+64	....	....
8.....	....	....	....	+95	+64	−31	+121	+80	−41	+119	+53	−66	+111	+29	−82	+77	+ 1	−76	+46	....	....

* A = Changes in blood sugar level (mg. per 100 cc.) when glucagon was administered alone.
† I = Changes in blood sugar level (mg. per 100 cc.) when glucagon was administered after insulin.
‡ A-I = Difference between values of A and I.

blood sugar changes from zero time level are given in milligrams per 100 cc. for the two groups of diabetic patients when glucagon was administered alone (A) and after insulin (I). In a separate column (A-I) the difference between the two values obtained in each patient is given.

A few patients with brittle diabetes showed early signs of hypoglycemic reactions (weakness, confusion, sleepiness, lag period in answering direct questions) at the end of three hours after the administration of 15 units of insulin and before the infusion of glucagon. One patient had an acute severe hypoglycemic reaction with convulsions one and a half hours after the insulin was administered. Glucagon was immediately given, and a few minutes later the patient recovered and was able to take some orange juice orally. The experiment on this patient was discontinued. All patients with brittle diabetes had moderate insulin reactions at the end of 90 to 120 minutes after glucagon was administered, and in four patients the experiment had to be discontinued before withdrawing the last specimen.

Figure 7 records the changes obtained in four patients with adrenal cortical hypofunction. In all cases the response was below the mean maximum change obtained in normal controls. All patients had early signs of hypo-

were 10 to 15 mg. per 100 cc. higher than those of the control experiments (glucagon alone) and the responses occurred in higher levels, but the magnitude of change

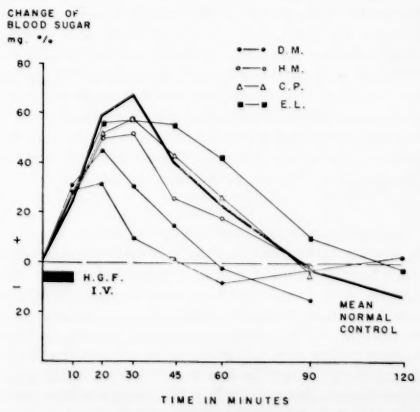

Fig. 7.—Response to glucagon in four patients with Addison's disease.

was of the same range. Figure 8 shows the responses of one patient with an islet cell tumor and two patients with functional hypoglycemia. The patient with the tumor fasted for only nine hours. Her fasting blood sugar level was 40 mg. per 100 cc. Twenty minutes after glucagon, it had increased 52 mg. per 100 cc. above the initial blood sugar value. After this peak there was a steep decline. The sugar value at 30 minutes was below the re-

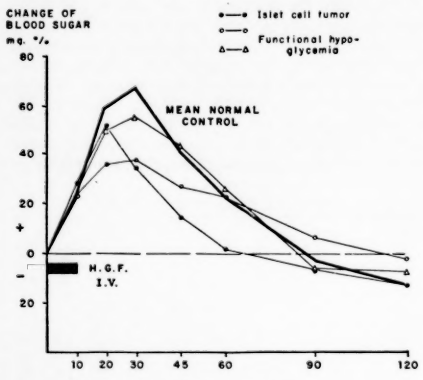

Fig. 8.—Response to glucagon in patients with islet cell tumor and functional hypoglycemia.

sponse obtained in 20 minutes. At the end of one hour her blood sugar values had returned to the zero time level and the patients showed mild hypoglycemic symptoms. The patients with functional hypoglycemia showed a decreased response to glucagon and gradual decline to preinfusion levels and did not experience any signs of hypoglycemic reactions.

Figure 9 shows the response to glucagon when it was infused three hours after the administration of 15 units of regular insulin to a group of patients known to be insulin-sensitive. In two of these patients total pancreatectomy had been done, in one subtotal pancreatectomy, and one had hemochromatosis. The patients in whom pancreatectomy had been done gave changes in the 20 and 30 minute specimens of the range of 76 to 84 mg. per 100 cc. One had decreased response to glucagon after insulin but not of the amount usually seen in patients with brittle diabetes. The patient with hemochromatosis had moderate response to glucagon.

COMMENT

Hyperglycemic Response in Normal Subjects.—The hyperglycemic response that was obtained in normal subjects for the dose of glucagon administered for 10 minutes is in close agreement with the response obtained by others [7] when a similar dose was infused for an interval of 30 minutes. Apparently, prolonging the infusion period does not increase the responsiveness to glucagon, as shown by the work of Van Itallie and others,[13] who obtained a fall in blood sugar values during a one hour continuous infusion of glucagon.

In the normal subjects studied the maximum hyperglycemic response was obtained 30 minutes after the infusion was started. This is similar to the findings of Kirtley and others.[7] Five of 10 subjects studied by Van Itallie,[13] receiving different glucagon doses that were given in different infusion times, showed a maximum response in 30 minutes. The importance of a preparatory diet for patients undergoing a glucose tolerance test has been emphasized in the past. One would expect on theoretical grounds that this should be true and possibly even more important for patients undergoing a test with glucagon, as it has been suggested that the height of the glucose response can be related to the amount of liver glycogen available. Pincus and Rutman [14] were unable to obtain a response to glucagon after a 96 hour fast in the experimental animal. We were unable to detect any change in the blood sugar values after glucagon administration in one of our patients who had fasted for 49 hours.

Hyperglycemic Response in Patients with Brittle Diabetes.—An increased hyperglycemic response was obtained in patients with brittle diabetes as compared to the effect in normal subjects or patients with stable diabetes. These results are not in agreement with the concept given by others [7] that patients with brittle diabetes possibly have poor glycogen stores. Furthermore, Bearn and others [15] found that in an insulin-sensitive diabetic patient, an aspiration liver biopsy specimen showed

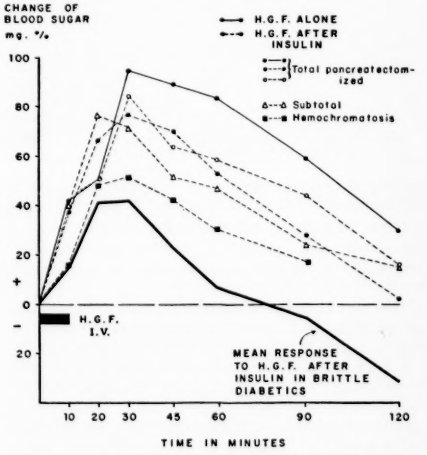

Fig. 9.—Response to glucagon in patients in whom pancreatectomy had been done and patient with hemochromatosis.

qualitatively normal glycogen content. Hildes and others [16] have shown quantitatively normal liver-glycogen in similar patients. On the basis of our results and the work of others mentioned, it would seem that liver-glycogen stores in patients with brittle diabetes are not depleted.

Since differences in response to glucagon were found in patients with brittle diabetes as compared to those

with stable diabetes and normal controls, and since it has been shown by the glucose-insulin tolerance test [2] that different response patterns to insulin are present in these two diabetic groups, study of the insulin-glucagon relationship in these patients appeared to be warranted. It was of particular interest for us to note that the increased hyperglycemic response to glucagon in patients with brittle diabetes was reversed in the same patients studied when glucagon was infused three hours after a small dose of insulin. Such a difference in response with and without insulin was not obtained in patients with stable diabetes or normal subjects. The planimeter readings were calculated (table 2) from the response curves by applying the method used by Himsworth and Kerr.[17] These are obtained by measuring with a planimeter the area of the curves up to 45 minutes. The area enclosed by the curve obtained after glucagon administration will be called the glucagon area (G area). The area enclosed when glucagon is administered after insulin, the glucagon-insulin area (G+I area), and the area enclosed between the G area and G+I area, which represents the action on insulin, will be called the insulin area (I area). The mean difference of the G area and G+I area was found to be 0.1 for patients with stable diabetes and 0.97 for those with brittle diabetes. The mean G/(G+I) ratio is 0.94 for patients with stable diabetes and 2.32 for those with brittle diabetes.

The unresponsiveness to glucagon after insulin in patients with brittle diabetes might be attributed to: (1) an antagonistic action of insulin to glucagon, (2) decreased liver-glycogen stores, (3) decreased glucose outpouring by the liver, or (4) increased peripheral glucose utilization. In vivo [18] and in vitro [19] experiments indicate that glucagon is an antagonist to insulin, but there is not general agreement on this point.[20] If one assumes that such an antagonistic action does exist for the doses of insulin and glucagon used (which when expressed in units is of the order 1:100 respectively), it is hard to understand why this does not hold true in patients with normal or stable diabetes. Since the dose of glucagon used is the same and the ability of the patient with brittle diabetes to respond to such a dose is present, one might conclude that the action of insulin per unit of glucagon has increased. The response curves to glucagon obtained in persons with brittle diabetes after insulin and in patients with islet cell tumor are quite similar. In the patient with the islet cell tumor, an excess of insulin is known to be present. Since this is not true for the patient with brittle diabetes, we believe that the similarity of the curves supports the idea of increased insulin responsiveness in patients with brittle diabetes.

The second explanation, that the decreased response to glucagon after insulin in persons with brittle diabetes is due to low liver-glycogen stores, seems unlikely on the basis of the increased hyperglycemic response obtained in the same patients after glucagon was given alone. It is possible, however, that increased peripheral utilization of glucose following insulin might decrease liver stores sufficiently to modify the response. In respect to the third possibility, Bearn and others,[15] by using the hepatic vein catheterization technique, showed that in patients with brittle diabetes the administration of insulin (0.1 unit per kilogram of body weight intravenously) resulted in a greater fall in the hepatic glucose output than that found in persons with stable diabetes or in normal subjects, which could explain the lack of response to glucagon in these patients. Evidence for the fourth possibility has been given by Himsworth,[21] who compared peripheral arteriovenous differences in the two types of diabetics during a glucose-insulin tolerance test. A significant increase of the arteriovenous differences in insulin-sensitive diabetic patients was demonstrated, indicating an increase in peripheral glucose utilization. Boller and Uiberrak [22] administered 100 gm. of glucose when hypoglycemic symptoms appeared, usually one and one-half to two and one-half hours after a large dose of insulin. In the insulin-sensitive diabetics, the orally given glucose resulted in a smaller hyperglycemic rise than in the insulin-insensitive group. These results could be explained on the basis of increased peripheral glucose utilization. In normal subjects a close correlation has been shown between the diminution of hepatic glucose output and increased peripheral utilization of glucose after insulin; thus it seems that both functions proceed at the same rate.[23] From these studies and others reported in the literature, it seems reasonable to postulate that in patients with brittle diabetes, insulin comes into action forcefully increasing peripheral glucose utilization and decreasing the glucose output of the liver.

TABLE 2.—*Planimeter Readings of Response Curves to Glucagon in Patients with Stable and Brittle Diabetes*

Patient	Glucagon Area, G	Glucagon Insulin Area, G+I	Difference	Ratio, G/(G+I)
Stable				
1.	1.6	1.8	+0.2	0.88
2.	1.7	1.6	−0.1	1.06
3.	1.2	1.4	+0.2	0.85
4.	1.4	1.3	−0.1	1.07
5.	1.8	1.9	+0.1	0.94
6.	1.9	2.2	+0.3	0.86
Brittle				
1.	1.4	0.9	−0.5	1.55
2.	2.3	1.0	−1.3	2.3
3.	1.5	0.6	−0.9	2.5
4.	1.4	0.7	−0.7	2.0
5.	1.1	0.7	−0.5	1.57
6.	2.3	0.9	−1.4	2.55
7.	2.8	1.5	−1.5	2.15
8.	2.9	1.9	−1.0	1.52

Which is the responsible mechanism for such an increased action of insulin is not clearly understood. There is no evidence at present that these patients have increased insulin sensitivity due to impaired pituitary or adrenal function. The insulin sensitivity in patients with adrenal failure has been postulated to be the result of poor glycogen stores.[4] If the insulin sensitivity of patients with brittle diabetes is due to impaired adrenal function, then a similar response to glucagon would be expected in both conditions. As this was not the case, we doubt if the adrenal gland is responsible in the insulin sensitivity of patients with brittle diabetes.

Himsworth,[21] from work done in the early 1930's, postulated that the action of insulin is conditioned by an unknown factor that makes the body sensitive to exogenous or endogenous insulin. This "sensitizing factor," when in excess, increases the rate of decline of glucose

per unit of insulin. This hypothesis possibly can be supported by the work of Mirsky [24] on insulinase and insulinase inhibitor, which may explain the mechanism of insulin sensitivity in patients with brittle diabetes.

Hyperglycemic Response in Patients with Other Metabolic Disorders.—Further experiments were done in patients with other metabolic diseases known to be insulin sensitive, in order to study the responses to glucagon in these conditions and to determine whether the mechanism of insulin sensitivity is the same or different in these patients. Four patients with adrenal cortical hypofunction showed decreased responsiveness to glucagon. Since cortisone in the experimental animal increases liver-glycogen and corticotropin stimulates the adrenal glands, increasing the output of glucocorticoids, it was

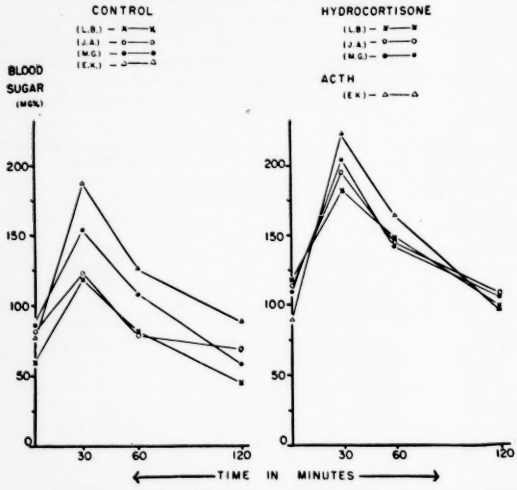

Fig. 10.—Results of glucose tolerance test in control patients and those given hydrocortisone or corticotropin (ACTH).

of interest to study the effect of corticotropin and cortisone on the responsiveness to glucagon in normal subjects and to compare the effect to that found in patients with adrenal cortical hypofunction. The experiment was outlined in the most simple manner in order to evaluate the possibility of its use as a clinical test for glucocorticoid production. In three normal subjects the responses to glucagon three hours after corticotropin were compared and only one subject showed a significant increase in response after corticotropin. Two patients with adrenal cortical hypofunction to whom corticotropin or hydrocortisone was administered in separate experiments did not show any consistent and significant differences from their control experiments. There was a slight increase in their preinfusion blood sugar values in all experiments. This is in close agreement with early work [25] in normal subjects, three of whom received 100 mg. of hydrocortisone intravenously for six hours while one received 40 mg. of corticotropin intravenously for 30 minutes. The results for the hydrocortisone experiments are compared to the results after a control infusion of 5% dextrose and 1% alcohol administered in the same subjects.

In figure 10 the results are given of glucose tolerance tests performed at the end of the six-hour control, after the hydrocortisone or corticotropin infusion had been started. The differences are more apparent during the glucose tolerance tests than in the fasting levels. Further work with other batches of corticotropin and other routes of administration is intended in order to elucidate the possibility of applying such a test as a diagnostic procedure. Engel and Scott [4] found no change in the response to an insulin-glucose tolerance test in patients with adrenal cortical hypofunction and panhypopituitarism when the test was repeated after a short interval of treatment with adrenal cortical extract.

At the time the present study was in progress there was a report by Helmer and Root,[26] who were studying the same problem in short-term experiments in animals. They found that long-acting corticotropin enhanced the hyperglycemic response to glucagon but cortisone did not have such an effect. Kerppola [27] found that epinephrine did not produce a greater rise in blood glucose levels in rabbits after cortisone. In longer term experiments De Boda and Altszuler [28] have shown that the administration of hydrocortisone to dogs in which hypophysectomy has been done not only raises the post-absorptive blood sugar level but also antagonizes the action of administered insulin.

Our experiments support further the hypothesis of Engel and Scott,[4] that an important factor in hypoglycemia unresponsiveness in patients with adrenal cortical hypofunction is the lack of adequate supply of liver-glycogen. The ability of these steroids to increase in a short interval of time the fasting blood sugar values, and to impair somewhat the glucose tolerance curve without increasing the responsiveness to glucagon, does show that their action in decreasing peripheral glucose use is rapid, compared to the increase of liver-glycogen reserves, and may be important in hypoglycemia responsiveness.

Two patients with functional hypoglycemia gave decreased responses to glucagon, and the decline of the blood sugar values to the preinfusion levels was not as rapid as that seen in a patient with islet cell tumor. The patients in whom pancreatectomy had been done and the diabetic patient with hemochromatosis known to be insulin-sensitive did not respond to glucagon after insulin administration, as patients with brittle diabetes did. This would imply that the mechanism of their insulin sensitivity may be different from that seen in patients with brittle diabetes. This is substantiated by the work of Volk and others,[29] who found by studying directly the insulin sensitivity of dogs in which pancreatectomy had been done that the rate of decline of the blood sugar level was similar to that found in normal dogs. Furthermore, Foa [30] has shown that the rise in the blood sugar level after glucagon is much greater in the dog in which pancreatectomy has been done whose condition is controlled with insulin than in the normal animal. Out of the three patients in whom pancreatectomy had been

done, two showed a greater rise with glucagon after insulin compared to their response when glucagon alone was given.

Glucagon in Patients with Insulin Sensitivity.—In the small group of patients with insulin sensitivity studied up to now, the diminished maximum response to glucagon when applied under standard conditions has been a consistent finding. Patients with adrenal cortical hypofunction, islet cell tumor, and brittle diabetes showed mild hypoglycemic reactions between one and one-half to two hours after glucagon was administered; these did not occur in two patients with functional hypoglycemia. Larger groups of patients have to be studied in order to evaluate the consistency of these findings. Blood specimens taken at zero time, at 30, and at 90 minutes possibly may suffice in evaluating the response to glucagon. This procedure seems to be simpler and safer than the insulin tolerance tests or their modifications

SUMMARY

The intravenous administration of a standard dose of glucagon was used as a test to study the hyperglycemic response of normal subjects and patients with various metabolic diseases who were known to be insulin-sensitive. In patients with brittle diabetes who were given glucagon, there was a distinctly greater rise in blood sugar levels than found in normal persons or patients with stable diabetes. In the same patients with brittle diabetes, when glucagon was given after a dose of insulin, there was comparatively little increase in the blood sugar level. In patients with stable diabetes and in normal subjects, on the other hand, glucagon given after insulin produced almost the same response as when glucagon was administered alone. In patients in whom diabetes developed after pancreatectomy, who were known to be insulin-sensitive, the response to glucagon given after insulin was not similar to that seen in patients with brittle diabetes or stable diabetes. In these two patients the rise in the blood sugar level was distinctly higher after glucagon following insulin than after the same procedure in brittle diabetes. In patients with adrenal cortical hypofunction (Addison's disease), islet cell tumor, or functional hypoglycemia, there was a smaller blood sugar rise in response to glucagon than in normal subjects. Pretreatment of normal or Addisonian patients with cortisone or corticotropin (ACTH) for a short interval did not influence their response to glucagon in most cases. From the small group of patients studied up to now, the application of the glucagon tolerance test seems a safe and practical procedure under standard conditions, and we believe that it could be valuable for the detection of insulin sensitivity in patients with hypoglycemia unresponsiveness, especially when an insulin tolerance test would be dangerous.

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EPIDEMIOLOGY IN OCCUPATIONAL MEDICINE

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A number of subjects suitable for this occasion were carefully considered and discarded before the final decision was reached to call attention to and to plead for recognition of the place and value of epidemiology in the field of occupational medicine. As a newcomer to the latter specialty who has served a long apprenticeship in the former discipline, the choice seems natural. At the same time, a limited experience with industrial problems ruled out any review or presentation of personal investigations for illustrations of its value to the average industrial physician and forced a general philosophical approach. Also, a naïve novice can easily be in error when he believes he has a greater awareness of the many and diverse opportunities to employ epidemiological techniques in the solution of industry's health problems, but, at the moment, it appears to be worth the chance.

Many may ask what is meant by the term "epidemiology," and where will it fit into the practice of occupational medicine? Knowledge of the cause and dynamics of any disease process is required for the determination of the importance of various factors, such as the host, agent, and environmental conditions, and for any estimation of the effectiveness of different control procedures. This background is assembled generally from three principal sources. The first of these is the detailed systematic clinical records of each of the syndromes as they occur in individuals presenting either apparent or inapparent reactions. The second is the study of the etiological agent, whatever it may be, either a living organism, its products, or a toxic material under experimental conditions in the laboratory. The third is the utilization of observations and analyses of the specific conditions associated with the occurrence of the disease and the causative agent in nature, or "epidemiological research."

EPIDEMIOLOGICAL METHOD

There is no desire to convey the impression that this approach has not been explored and utilized in the past in the solution of industrial problems. Many classic examples come quickly to mind. The mercury poisoning of felt makers, the scrotal cancers of mule spinners, the skin cancers of shale-oil workers, and similar investigations indicate the wide variety of such efforts found in medical literature; however, interest in the use of the epidemiological method in studying not only occupational but infectious diseases declined with the development of the apparently more direct and concrete experimental techniques. Yet some of the very fundamental relationships to be taken into account in the formulation of control procedures are not even revealed, much less explained, by these methods. They can be elucidated and

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understood only by the systematic investigation of the various syndromes as they occur in nature, that is by the epidemiological method—not attempting to supplant but rather to supplement and confirm the results obtained under the obviously artificial conditions required in the laboratory.

Three decades ago, during the formative aspects of organized educational efforts in public health, Frost [1] recognized that workers in preventive medicine were obliged to understand and use epidemiological methods systematically in order to plan and guide their administrative practices effectively. In a plea for support of "epidemiological research" by public health agencies, Frost emphasized the point that they dared not shirk this task. Because of their access to epidemiological data, these groups have a very special opportunity and responsibility for the development of such knowledge and the very science itself. Only in this way could public health agencies be expected and prepared to: (1) meet community demands for the diagnosis and control of endemic and epidemic disease, (2) make intelligent compilations and interpretations of records too often considered solely and primarily administrative, (3) extend knowledge beyond the bounds of clinical and experimental medicine, and (4) take as their ultimate objective the prevention of all kinds of disease.

INDUSTRY'S RESPONSIBILITY FOR RESEARCH

The central theme of this presentation is to indicate that industry and its medical departments must accept the same responsibility for epidemiological research on similar grounds. Again, there is the unusually easy access to detailed epidemiological data, the routine compilation of administrative records, and the growing recognition that the practice of occupational medicine can only be appraised and guided by such analyses. Also, there is now general acceptance by the medical profession that the goal of occupational medicine is primarily preventive rather than therapeutic. There is also a unique opportunity in industry to advance the specific knowledge of the effect of diverse toxic materials on man under widely varying and yet relatively well controlled conditions of exposure. The industrial population of today is made up of groups subject for a definite period of time to hazards that can be defined with reasonable accuracy. In this respect, this ability to describe "exposure" gives the investigator of occupational problems a tremendous advantage over the student of infectious disease. Furthermore, the composition of the population subject to risk can be far more readily described with greater preciseness in respect to many important variables such as race, sex, and chronological and industrial ages.

On the other hand, the reasons for an immediate and unqualified acceptance of responsibility for fundamental and extensive investigations in this field multiply and become more urgent day by day. New processes, new compounds, and new applications are developed continuously. These create intramural problems not only for industry but for the outside environment as well, both near and far. For example, the safe and practical disposal of wastes, liquid and air-borne, has become a complex and serious question. The widespread use of pesticides introduces other complications. It is now evident that industrial hazards have spread far beyond the confines of the plant, and industry is compelled to consider the impact on the community as a whole. This involves not only acute reactions but also the possibility of long-range changes. All this adds up to the inevitable demand for additional epidemiological research.

DEFINITION

What is included in "epidemiology?" Correctly defined, it is "the sum of human knowledge of epidemic diseases." It is true the content has drifted far from this meaning in modern usage. The application is no longer restricted solely to epidemics or even to the endemic incidence of infectious disease. On the other hand, the term as actually applied does not imply that this science or art represents essentially a specific limited body of medical knowledge as, for example, is found in other disciplines such as pathology, pharmacology, and bacteriology. The most proper definition is: "that branch of medical science which deals with the characteristics, etiology, and mode of transmission of diseases as indicated by the circumstances and conditions of their occurrence in nature." Corresponding to this interpretation, the epidemiology of a disease is: "the characteristics of that disease with respect to the conditions and circumstances of its occurrence in nature."

Although originally concerned solely with the explanation of the cause of epidemics, the term "epidemiology" of necessity had to become more inclusive. An epidemic is customarily described as an unusual increase in incidence or in the actual occurrence of disease. To explain epidemics, or even long-time trends, it is essential to understand the factors and the relationships that determine the usual levels of prevalence and characteristic distribution of diseases in the population. The term can also be broadened and applied essentially to similar studies of acute diseases in animal and plant populations.

RELATION TO OTHER FIELDS

The successful use of this approach in the solution of infectious disease problems has been followed by its extension to other health fields. It is recognized now that epidemiological techniques can be adapted with profit to the study of chronic diseases, acute toxic problems, nutritional deficiencies, accidents, and mental disease. These methods also have proved invaluable in assaying the effect of preventive procedures such as mass immunization, chemoprophylaxis, dust control, and similar protective efforts. How and in what ways is epidemiology related to other aspects of medical science? Any complete understanding of a disease process, its nature, etiology, relative importance, and control requires information from four aspects. The first necessity is a knowledge of the reaction of the individual. This is the contribution essentially of clinical medicine and pathology. Second is a knowledge of the pattern of occurrence in the population. This includes a description of the frequency and distribution of cases or deaths in various groups and is obtained through the routine

1. Frost, W. H.: The Importance of Epidemiology as a Function of Health Departments, M. Officer **29**: 113-114 (March 10) 1923.

compilation of records. Third is a knowledge of the specific causative agent and its behavior under controlled conditions. This includes its biology, if it is a living organism, or its chemistry, if it is some inorganic or organic compound. This is the province of the experimental laboratory, either of microbiology or toxicology. Fourth is a knowledge of the significant relations between the occurrence of disease in nature and the complex, almost innumerable conditions—intrinsic, environmental, and occasionally special—that affect not only individuals but different segments of the population. It is at this point that epidemiology comes into its own, and this is the justification for considering it as a special discipline of medical science.

Epidemiology depends, therefore, upon clinical medicine for the recognition of disease, upon the experimental laboratories of pathology, microbiology, and toxicology for the evaluation of certain significant biological factors, and upon vital statistics for the description of the pattern of occurrence in the community. It is essentially the connecting link, assembling and employing the observations from each of these fields, first for analysis and subsequently for interpretation. It is likewise better to look upon it as essentially an inductive science concerned not merely with describing the occurrence and distribution of disease but equally or more involved with fitting the observed pattern into a consistent practical philosophy.

CHARACTERISTICS AND FUNCTION

It will be worthwhile at this point to review briefly how this is usually accomplished. Generally, the epidemiological characteristics of clinical reactions resulting from industry or community exposures to toxic materials, as with infectious diseases, are as difficult to enumerate and classify as their symptoms and usually have been much less well thought out. Some of the essential ones, expressed in simple rather than scientific terms are: the area of occurrence, the manner of occurrence, and the selection in relation to simple variables as race, sex, age, and environmental factors. These can be summed up simply as "when," "where," and "in whom." Much more complex and diversified are the specific characteristics. Some of these are: the relationship of individual exposure, and the relationship of personal habits, nutrition, economic status, previous illnesses, physical defects, and like variables.

However, as indicated earlier, the function of epidemiology lies not in the simple enumeration but rather in the reasonable, logical interpretation of both categories of characteristics. To do this, if the industrial physician is to take advantage of the application of epidemiological methods in his particular situation, the requisites are: (1) knowledge of the essential facts and principles of experimental pathology (etiology, toxicology, microbiology), (2) at least an elementary knowledge of the use of quantitative methods in biological studies, and (3) knowledge and experience in clinical medicine and diagnosis.

It must be acknowledged that significant contributions can and have been made by a clinician with no great knowledge of the statistical method and by a good statistician with but a limited knowledge of clinical medicine or toxicology. Generally, it is essential and desirable that the skills as listed be readily available and accessible. Also, the epidemiologist must acquire, both by training and experience, a frame of reference related to those facts that he is handling for orientation and comparison. He must acquire a technique, not entirely as a routine but rather as a uniform method of collecting and analyzing his observations, based upon definite principles, such as a clinician employs in his study of a patient. In other words, he must develop the habit of thought, the philosophy, and the pattern of approach that are necessary to comprehend the problem, to plan the collection of additional material, and to interpret the data.

CAUSATION AND CONTROL OF DISEASE

For the analyses, there are certain basic principles in epidemiology as in the other branches of medical science. To illustrate, two conditions are essential in the causation of disease, namely: exposure, that is to say effective contact between the specific agent and the host; and susceptibility on the part of the host. Prevention lies in controlling one or both of these factors. Satisfactory control is rarely obtained by a specific prophylactic procedure in dealing with an industrial problem but is generally achieved by modifying the environment or the habits of the workers; hence the requirement to know as accurately as possible the importance of various relationships in the actual environment to the occurrence of disease. The appearance of a case is tangible proof that the essential conditions of exposure and susceptibility have been fulfilled. Nonoccurrence in another worker may be due to: lesser or no exposure; lesser susceptibility, specific or structural; or chance, such as accident of lodgment or the physical characteristics of the material. These factors are indeterminate in the individual and are subject to all degrees of variation. Between two individuals, the investigator can draw no conclusions as to their relative exposure or susceptibility, since there is no workable basis for comparison. He is forced to accept the fact that causes apparently equal need not produce the same effect.

If adequate-sized groups of individuals are considered, the situation is quite different. Significantly different incidence rates in the two samples will indicate a noteworthy difference in exposure, susceptibility, or both; hence, the first fundamental principle is that of comparison of the incidence rates of disease in groups, known as selection. In general, a direct comparison is the simplest and most readily understood expression of association. Certain precautions are essential in any application of this principle to epidemiological data: 1. The variables should have some presumptive relationship to the incidence of the clinical reaction. 2. The assumption that the groups are otherwise similar must be justified by collateral information. 3. The observed differences must be statistically significant. The second cardinal principle is that of composite proof. The underlying concept is that the probability of two independent events occurring at the same time is the product of their separate probabilities. This method is instinctively applied in reasoning without mathematical knowledge and frequently is applied to events that are beyond mathe-

matical expression. It is involved in the validity of circumstantial evidence in general. The application in epidemiology is in testing and excluding various hypotheses rather than proving any specific one. These principles are of general and universal application and are capable of infinite combinations. They can be utilized to explain causation of a simple epidemic of food poisoning or to explain the etiology of cases arising from long exposure to complex materials.

NEED FOR MORE COMPLEX STUDIES

A final question may be raised as to what additional information can be gained by developing and applying epidemiological methods in industrial medicine. Accurate, relatively simple observations have proved to be one of the strongest assets of preventive medicine in its efforts to control infectious disease. For example, it has been found comparatively easy to win support for the protection of water, food, and milk supplies, for vaccination against smallpox, and for diphtheria immunization because it has been possible to present convincing evidence of the efficacy of such measures. Similar studies in the field of industrial medicine, particularly in dealing with plant exposures to toxic materials, have proved equally valuable.

However, health workers long ago realized far more complex studies must be undertaken to answer such queries as: "What effect does isolation of a recognized case of infectious disease have upon the total incidence in the community?" or, turning from morbidity to mortality, "What proportion of deaths from a given disease could be prevented by improved health education or better hospital facilities?" The variables to be considered for the solution of such problems obviously are far too complex for any experimental laboratory. Similarly, industry and the industrial physician are confronted by questions of equal complexity and difficulty. For example: "What is the maximum permissible exposure to a toxic material, not in any etiological relation to an acute reaction but as a possible cause of disease, 10, 15, or 20 years later?" or "What will be the effect of measures designed to limit exposure to a given material, either in degree or kind?"

The present lack of uniformity and the all too frequent halfhearted manner in which recommendations for the control of occupational hazards are received is sufficient proof that this additional knowledge is needed. It can be admitted that a more complete understanding might not be encouraging or even occasionally resisted, since it may point to the desirability of abandoning some of the more cherished practices of certain industries. From the other side, it should be apparent, even to the most skeptical, that this insight would stimulate the formulation of new defense procedures and finally lead to a more effective administration of control activities. Again, it must be emphasized that such information can hardly be secured entirely by experimental toxicological investigations or by more elaborate analyses of the necessarily simple data drawn from crude mortality and morbidity statistics. Acceptable solutions can be found only by making detailed, organized studies of the circumstances and conditions under which cases and deaths actually occur in nature and by recording, analyzing, and comparing disease incidence, taking into account all of the pertinent variables. This is particularly true when the industrial physician is concerned with the possible hazards of years of exposure to low levels of concentration.

NEED FOR NEW METHODS AND TECHNIQUES

As noted in the introduction of this presentation, industrial medicine offers innumerable opportunities to utilize the basic principles of epidemiology not only for the solution of specific problems but to make notable contributions to the knowledge of man's reaction to pathogenic materials in his environment. New methods will have to be developed and old techniques modified. Among the greatest needs in this field are methods that can be readily employed in the elucidation of the relationships between the occurrence of human disease and chronic exposures, either in the plant or the community, for example, to small amounts of possibly noxious materials, regardless of the vehicle, be it air, food, or water. The unfortunate situation confronting the investigator is that the few techniques that have been proposed for the study of chronic infectious diseases have never been completely evolved or perfected. It is more than likely, therefore, that provision for additional training of specialized investigators for this field will be required not only in schools of public health but also in institutions primarily concerned with the techniques and procedures of industrial hazards. Additional facilities and support may have to be found.

SUMMARY AND CONCLUSIONS

In summation, the stimulation and participation in this type of medical research must be considered and accepted as a unique and peculiar function of the industrial physician because: (1) such investigations approach the problems of industry and now the community from precisely the angle of the most direct interest to him; and (2) he and his department have a virtual monopoly on the facilities and records required for systematic studies in this field. There is no great need to organize or support a specially qualified group of workers. In the modern medical departments found in industry today, mechanisms have been perfected for the prompt notification of cases, for periodic examinations of the workers, and for control of the working environment. Very frequently, this supervision can be extended into the home. This ability to control the conditions found in any given situation is almost unparalleled except in military or penal establishments. It must be recognized that a plant population can be followed even more closely than school children, the traditional subjects of the public health worker. Furthermore, through the routine checkups, individuals without disease can be studied as carefully as those presenting clinical symptoms, something always sought but rarely achieved in epidemiological research in the general community. Independent institutions, academic and otherwise, cannot provide this machinery and staff on any comparable scale. Governmental agencies such as health departments, with limited budgets and faced with the fear of regulation on the part of industry, have likewise no real opportunity to work in this field and frequently are denied access to it. The individually interested physicians, at one time leaders in

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epidemiological investigations of infectious disease, are completely shut out.

To measure up to this responsibility and to take advantage of this unrivaled opportunity to make significant contributions to the science of medicine, the industrial physician needs only to recognize that undertaking such investigations is an essential part of his activities. Next, some definite specific problem suitable to the situation and facilities should be selected, and, with this in view, the routine procedures, records, and tests can be organized in a fashion to permit the easy assembling of concrete information bearing directly upon the problem. Finally, it will be necessary to methodically compile these data and to make the answers available to others. The proof that an active, interested industrial physician and his staff have the necessary resources for fruitful studies of which any research organization might well be proud has been repeatedly demonstrated. Many of the simpler questions, those that require less rigidly controlled observations, have been answered. Those that remain may require a somewhat greater effort, but there are many questions that may be readily solved simply by more effective exploitation of their opportunities by industrial medical teams.

THE CIVILIAN DOCTOR AND OUR FUTURE SECURITY

Isidor S. Ravdin, M.D., Philadelphia

I am grateful to the members of this section for having honored me with the Chairmanship during this session of the American Medical Association. The splendid attendance at this meeting is ample assurance that the Medical Military Section of this Association is on a sound footing. If such a section had been organized and functioning 40 years ago, civilian medicine and military medicine would perhaps have reached sound understanding many years ago. The problems that concern civilian doctors and their counterparts in military life are many and varied. The experiences of the last decade have demonstrated that they are often not easily solved to the complete satisfaction of both groups. There seems, at the present moment, to be no way to achieve the necessary goals without pro'onged discussion, which, at times, leads only to the multiplication of differences of opinion. Many of the present opposing concepts are without clear meaning, and many of the arguments are poorly conceived, perhaps even selfish in their origin. Yet, by one means or another, a meeting of minds must be achieved. Agreement on many matters is not only highly desirable but, in the present state of world affairs, vitally essential, if we are to command respect from our people and if democracy is to survive in the areas in which it now functions.

MANPOWER REQUIREMENTS OF MEDICAL MILITARY SERVICES

A few weeks ago I received a letter from one of my residents who is now on duty with our forces in Germany. Although he has had several years of residency training in surgery, he is now not so assigned. In his letter he said, "Though I have said it before, I want you to know that whatever my assignment is to be, I will do the best I can. The government allowed me to finish my internship and some of my residency. I wasn't taken during the Korean War. I am here and have my wife with me. Of course, I would like to do surgery—but I know I owe the government and the Army more than they owe me. A brief glimpse of these European countries makes it very clear that two years of service is a small price to pay for being an American citizen."

It cannot be doubted but that this young man has a high respect for our democratic institutions. The importance of this type of approach to obligatory military service should be obvious to everyone who treasures our way of life, and yet many men, young and old, fail to understand it. Some of the present difficulty lies in the disinclination to trust the statements that have been made by one group or another. Unless concerted action is taken to achieve unity of opinion, the position of medicine as a whole in our country may be jeopardized, and the public may well question the motives of the leaders of civilian and military medicine.

There exists an actual distrust of the requested manpower requirements of our medical military services. There are some who have come to a fixed opinion that the medical services of our armed forces are already greatly overstaffed; that medical personnel is too frequently poorly assigned, not because of necessity, but because of faulty administration; that the medical care in the armed forces could be better met by a unified medical service; and that the dependent care problem has been created in order that more civilian physicians and dentists be forced to active duty.

We must, in the shortest possible period of time, reach sound decisions on these matters. We must carefully and unselfishly scrutinize them and come to agreement on what is important for adequate medical care for our military forces and their actual dependents and, at the same time, what is essential for adequate civilian medical care. Only by taking a broad and unbiased view of the over-all situation can a solution be reached that will be equitable to all concerned. We must find an appropriate balance for these controversial matters. We cannot achieve this by one group preaching to the other. We cannot achieve the unity we need by political action. We will achieve it only by a meeting of minds and by a sympathetic understanding of the complicated problems that concern civilian and military medicine. The solution will be achieved more easily if all agree that everyone concerned has a high regard for our democratic processes and all are equally interested in the preservation of our national integrity.

Chairman's address, read before the Section on Military Medicine at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 7, 1955.

It cannot be possible, as some have intimated, that doctors have lost so much of their social consciousness that they fail to realize that, if freedom is to live, physicians, who represent an important segment of those with disciplined minds, must assume leadership much more broadly than they have in the past. We must demonstrate to a greater degree than ever before that, while we have acquired certain skills during training and practice, we have maintained and strengthened the important qualities of citizenship in a democracy. Elliott Dunlap Smith of the Carnegie Institute of Technology stated a few years ago, "Our complex and far-flung democracy is a democracy of men who work. Unlike the democracies of the past, it has no leisure class which is its governing class. If its inherent freedom is to survive, its keenest and most disciplined minds—and by and large this means its professional men—must devote their moral energies and their intellectual powers to become leaders in solving its problems." One of the basic points in this important statement, to my mind, is the implication of voluntary leadership, and an unwillingness to be exploited does not in any way mean an unwillingness to assume leadership.

"DOCTOR-DRAFT" ACT

The House Armed Services Committee is now considering an extension of the "Doctor-Draft" act. Quoting the American Medical Association Washington Letter of April 29, 1955, "The American Medical Association has registered with the House Armed Services Committee its opposition to a two year extension of the Doctor Draft Act, scheduled to expire next June 30." There are those who find themselves in agreement with the Trustees of the American Medical Association. Some of the members of the Health Resources Committee of the Office of Defense Mobilization have also stated that an extension of the "Doctor-Draft" act at this time is unnecessary. On the other hand, the Secretary of Defense of the United States and the Assistant Secretary of Defense (Health and Medical) believe that adequate and necessary medical service cannot be provided our troops unless the act is extended. All of those vitally concerned with this problem are men of integrity. All of them have had the same data upon which to base their opinions. In spite of this, they have not been able to come to a uniform decision and to appear before the Congress and defend a unified concept. In the final analysis, the decision should be made on the basis of our national interest and security. Private interests should not be considered. I say private interests to include the civilian physician on the one hand and the military physician on the other. The democratic impulses of either group will not be strengthened if undemocratic motives are used by one side or the other.

I am sure that the decision of the Trustees of the American Medical Association and certain members of the Health Resources Committee were not made in their self-interest. They would not capriciously jeopardize our national security, and yet equally honorable men who are spending a part of their lives in government believe that it is of major importance that the act be continued. We must assume that all of those concerned in this matter are equally concerned with strengthening the integrity of our democracy, and yet we must face the fact that there exists a sharp difference of opinion between those representing civilian medicine and those representing military medicine. The continued strengthening of American medicine will not be achieved without careful consideration of our complete responsibility in public service. Carl H. Appleby in a somewhat similar situation gave the following admonition: "In this pursuit there must be care not to confuse one's professional viewpoint, functional preoccupation, or personal prejudices with the public interest."

This nation has always been proud of the type of medical service that has been provided our military forces. Today, as never before in the history of our country, our troops are to be found throughout the world. The Army and the Air Force are dispersed over a large part of the earth's surface. Our Navy will be found over the seven seas. For the troops of these supporting and defending services, doctors must be provided. A large segment of these forces are individuals who have been drafted from civilian life. The majority do not seek a career in the military forces. They must be provided adequate medical service, and this must be achieved within our democratic processes. I am sure that all of us agree that there cannot justifiably be two standards of medical service—one for those in civilian life and one for those who, because of desire or because of necessity, serve in the armed forces for variable periods of time.

The letter that I read from the young resident who is now serving in Europe exemplifies, I am sure, the patriotic spirit of the great majority of our young graduates. The polemic that now faces American medicine in this matter cannot be resolved merely by insisting that physicians be brought into the services through the regular draft act and not through special legislation. One of the codes of ethics of the American Medical Association might well be repeated here, "A profession has for its prime object the service it can render to humanity; reward or financial gain should be a subordinate consideration." Later it states that the principles laid down for the guidance of the profession "are primarily for the good of the public." Accepting the fact that the medical profession has for its prime object the service it can render to humanity, we must also accept the fact that this Association has in the past been able to adjust the particular interests of its members to the common interest of the nation. It is of primary importance that our concept of service not be muddied by a momentary bias, for such an approach by either group is unhealthy for our national security. Everyone concerned is agreed that civilian physicians must, as long as our democratic processes are threatened, assist in the medical care of the troop strength authorized by our government.

CIVILIAN DEFENSE PROGRAM

I am concerned by another matter that involves our national security equally as much as does that which I have been discussing. I refer to the civilian defense program and the part that doctors are playing in it. It has been said by many who have looked into the matter that, should we again become engaged in war and should modern methods of destruction be utilized, our civilian population would suffer as much, or more, in the form of major injuries as would our military population. Be-

tween our military forces and our civilian population, we may well encounter casualties in numbers previously undreamed of. Civilian defense is being planned on a relatively local basis, and yet, should we become involved in a major conflict, the doctors of many of our communities will suffer as many casualties as will the cross section of the community. How, then, can they be expected to provide the medical support that will be needed under such circumstances? We shall have to be prepared to transport doctors representing all facets of medical training from distant sites to provide medical care for those whose communities have met a devastating attack.

We shall, in all likelihood, have to supply also medical and surgical supplies in undreamed of amounts. We shall have to supply nurses and orderlies and all of the other supporting framework that goes with our concept of modern medical and surgical care. We shall have to supply blood and plasma substitutes in unparalleled amounts. We shall have to have people trained to administer these substances. Here lies a field of service so urgent and so great that our national safety may well rest on the manner in which it is carried out and the speed with which such care is expedited. We must ask ourselves whether we shall continue to go on living in a fool's paradise or whether we will face this important problem seriously and begin to plan for supported action on the broadest possible basis.

It is the opinion of many who know something about these matters that our civil defense program will fall far short of the exigencies of the situation and that the only way in which the matter can be expedited adequately will be by some type of military control. Can this be better achieved by those who have never had military training or by those who have had a background in the authority and discipline that military training encompasses?

Civilian medicine must actively concern itself with this great problem. It must think as Plato thought when he said, "But that we shall be better and braver and less helpless if we think that we ought to enquire than we should have been if we indulged in the idle fancy that there was no knowledge and no use of seeking to know what we do not know—that is the theme upon which I am ready to fight, in word and deed, to the utmost of my power." We cannot think of the possible catastrophic destruction without realizing that our national security, under such circumstances, may well be decided by the activity of civilian medicine. We cannot think of this matter in terms of 30, or 20, or even 10 years. We shall have to use our talents as never before. We shall have to use them swiftly and courageously. It is only by being adequately motivated and properly trained that we can calmly and understandingly carry on in the event of a great emergency.

What is considered the ideal type of practice for a given injury in civilian life may not be possible under conditions of military action where thousands of casualties are concerned. There will be those who will have to make the decision as to who is to wait and who is to receive immediate care and who will die without care. They will have a great responsibility, but such decisions must be made under conditions of mass casualties. These decisions will be made best by those who have had the opportunity to face the problem. The best care will be given by those who have been trained not in the traditional methods of care but in the emergency methods of care, for, in the words of Jacob Bigelow, "He will then interfere or he will wait, he will act or he will forebear, as he only knows how who can form a correct verdict from the evidence before him, and knows the immeasurable good or harm which hangs on medical practice."

The only way the civilian doctor will surmount the difficulties associated with the many casualties that will occur in future catastrophies of warfare will be by having the wisest type of leadership in medicine. We will not achieve success by last minute attempts to solve the problems that will present themselves. If such a circumstance occurs, catastrophe, as we have never known it before, will follow. If we plan wisely and plan harmoniously, we will be ready to meet any emergency that may arise. Civil defense on a local or even a regional basis is, in my opinion, unrealistic. We must develop a plan that will permit the transfer of those concerned with medical care from distant areas and the assignment of those available at the local level. Whether these individuals will be under complete civilian control or whether they will, once they are called to duty, be under military control should be decided before the emergency arises. What needs to be recognized now is that they must be under some type of disciplinary control. The future can not be left to chance. The medical profession, both civilian and military, must not be a party to any action that undermines the faith that the civilian population has traditionally held in us.

Recently, Major Gen. Paul R. Hawley testified before Congress that the civilian physician, under inadequate disciplinary control, might not, in the event of serious catastrophe, attempt to find his way to the point of his assignment but that he might well attempt to find his way to his home to see what had happened to his family. If the fields of future activity are clearly delineated and each man not only knows his point of assignment but knows what will be expected of him, he will know which way to go in the hour of trial.

DEPENDENT CARE PROBLEM

These are but a few of the problems in which the civilian doctor must play an important role in the maintenance of our national security. The dependent care problem is perhaps equally important. An equitable solution to this problem is not at the moment at hand. It will not be solved merely by stating that the families of our military forces should remain at home during long periods of what actually amounts to an armed truce. It will not be solved by insisting that dependents should be taken care of in civilian institutions and by civilian physicians not on military duty. It will be solved only by a clear concept of this great problem and by the united willingness of physicians, both civilian and military, to meet it. A great majority of those now serving in our military forces are individuals who have come from civilian life and intend to return to it. I have been careful to observe that when my residents and assistant residents go on active duty they take their families with them. The many other nonmedical personnel wish to do likewise. We should not during this period deny them

this privilege. They have every right to expect care not only for themselves but for their dependents. How this should be provided and where it should be provided is the matter that needs solution. The responsibility is not alone a military one. It is a responsibility of medicine as a whole, and it can and will be, I am sure, equitably met.

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CLINICAL NOTES

INSULIN COMA THERAPY IN ADVANCED PREGNANCY WITHOUT HARM TO MOTHER OR CHILD

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and
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Only a few cases of insulin shock therapy during pregnancy are reported in the literature. Goldstein, Weinberg, and Sankstone [1] reported the employment of insulin subcoma therapy on 13 treatment days, following a course of pentylenetetrazol (Metrazol) convulsive therapy, without harm to the child. Although their description does not mention just when in the course of the pregnancy insulin was used, one infers that it was after the gestation was at least four months advanced. McConnell [2] in 1945 mentioned two cases: insulin coma therapy was started when one of the patients was 10 weeks' pregnant and the other 14 weeks' pregnant. Neither showed any abnormal symptoms during treatment, and both delivered normal babies. One of these children was 9 months old and the other was over one year old at the time the paper was written. On the other hand, Gralnick [3] had less fortunate experience with two patients treated by means of insulin-induced coma; each gave birth to a dead fetus at term. In the first case, treatment was begun when pregnancy was about two months' advanced and included 14 coma sessions ending early in the second trimester; at term the patient delivered a macerated fetus weighing 17 lb. (7,711 gm.). The second patient in Gralnick's report received electric shock therapy about a month after becoming pregnant, followed by insulin shock therapy initiated when she was about two months' pregnant. The 18 sessions of the latter therapy resulted in eight comas and were discontinued shortly after the start of the second trimester. At apparent term, this patient suddenly went into labor and delivered a macerated fetus weighing 7 lb. 10 oz. (3,459 gm.). Kent [4] reported on the case of a paranoid schizophrenic patient whose pregnancy terminated in delivery of a normal infant. This patient received during the fifth, sixth, and seventh months of gestation treatment with insulin on 90 days and 20 electroconvulsive treatments.

From the Stritch School of Medicine, Loyola University (Drs. Luhan and Tuteur) and the Illinois Department of Public Welfare, Elgin State Hospital (Dr. Tuteur).

1. Goldstein, H. H.; Weinberg, J., and Sankstone, M. I.: Shock Therapy in Psychosis Complicating Pregnancy: Case Report, Am. J. Psychiat. **98**: 201 (Sept.) 1941.

2. McConnell, J.: Two Years' Experience of Female Schizophrenics Treated by Insulin Coma Therapy, J. Ment. Sc. **91**: 506 (Oct.) 1945.

3. Gralnick, A.: Shock Therapy in Psychoses Complicated by Pregnancy: Report of 2 Cases, Am. J. Psychiat. **102**: 780 (May) 1946.

4. Kent, E. M.: Shock Therapy During Pregnancy, Psychiatric Quart. **21**: 102 (Jan.) 1947.

REPORT OF A CASE

The patient was a 22-year-old woman, native-born of Polish stock, the third in a sibship of seven. There was no family history of mental illness. Her parents had little time for her during her developmental years. She completed high school and then worked as a comptometer operator, continuing at this for two years after her marriage, which occurred when she was 17. She had received no sexual instruction from her parents. Her entire family was opposed to her marriage because the husband was not Polish and was considered to be domineering. She had become somewhat estranged from her family since her marriage. There was one child, a boy 3 years old, whose delivery was by a difficult breech presentation. The patient was described as a quiet, shy, sensitive, moody, and meticulous person, who confided very little in her husband or relatives, had few friends, and at times was given to daydreaming. For the past two years, her husband had been half owner of a truck-painting business. The patient was very resentful because he spent long hours at his work, and she disliked his business partner, who was known for his marital infidelity. After the patient became pregnant a second time, she pleaded with her husband to give up his business, and heated quarrels over this became increasingly frequent. It was the husband's impression that she feared the pending second delivery because of the trying experience with the first, and as the pregnancy advanced she wished that she would miscarry. When she first learned that she was going to have another child, she became depressed, quiet, hard to get along with, and resentful of her husband. However, when quickening occurred, she felt better and visited her parents in Wisconsin but while there was seclusive. About 10 days before admission to the hospital she called her husband, asking him to come home from work because she thought she was going to have a miscarriage. When he arrived she said that she had already lost the baby, spoke incoherently, and stayed up until 4 a. m. She tore things from the dresser drawers and wanted to return everything that anyone had ever given her. She remarked that her husband was not providing enough for them to live on and was not giving her what she wanted. After this episode she stopped doing the housework and neglected their 3-year-old son. She thought people were looking at her and crying because she was dying. She felt there was no hope for her and it was too late for help, all through the fault of her husband. She said over and over again that her husband left her when she needed him most. She slept very little and ate poorly. The patient would remark that she was hungry, look down at her abdomen, and then say that she was full. She considered sedatives prescribed for her to be poison and thought that if she went to the hospital she would be embalmed.

The patient was admitted to Loretto Hospital on May 14, 1954, where she was treated by one of us (J. A. L.), receiving 19 electric shock treatments and 8 insulin subcoma treatments, the latter produced by doses varying from 25 to 80 units of regular insulin per session. The insulin therapy was begun on June 3, 1954, in the third trimester of gestation (delivery occurring on Aug. 10, 1954). On admission to the hospital she appeared confused and bewildered, said that "they" were laughing at her, spit out medicaments, and became combative. She was noisy; laughed inappropriately; yelled, screamed, or sang from time to time; and maintained she was having a miscarriage. There was involuntary urination. She remained agitated and disturbed in spite of electroconvulsive treatment and sedation and showed no significant improvement after eight subcoma insulin treatments. At night she experienced visual hallucinations and, if not restrained, often tried to crawl under the bed in response to fearful hallucinations that men outside her window were coming in to attack her. A diagnosis of severe schizophrenic reaction of a mixed type was made.

On June 11, 1954, she was transferred to the Elgin State Hospital as a voluntary patient, where on admission she was found to be seven months' pregnant. While she was friendly and contact was easily established, she immediately impressed

the examiner as immature and childish. She related an alleged experience she had prior to being transferred to this hospital, saying two men came into her room at Loretto Hospital one night, climbing up a tree and entering through a window, however, not raping her. An inappropriate laugh accompanied this description. Several days after admission she became extremely agitated, confused, and was very frightened. At times she would ask the examiner if she was alive, but at other times she was able to discuss matters coherently.

On June 14, 1954, subcoma insulin therapy was resumed, beginning with 15 units the first day and 20 units the following day. The patient remained fearful and tremulous, was confused most of the time, and wandered about the ward. On June 21, 1954, she was started on insulin shock therapy, beginning with the administration of 20 units. This was eventually increased to 280 units but then decreased gradually to 170 units. On Aug. 10, 1954, at 12:30 a. m., the day she was to receive her 38th treatment, she delivered a full-term baby weighing 7 lb. 4 oz. (3,289 gm.).

The patient had received, prior to this, a total of 37 insulin shock treatments, with 26 comas and no seizures. Her last treatment prior to the delivery was on the day before, Aug. 9, 1954, and terminated at 11 a. m. During the course of treatment the patient began to dress more neatly and seemed more cooperative. Her apprehension abated; at times she was euphoric and confused, but she became more interested in her surroundings. On July 11, 1954, a relapse occurred during treatment. She became again confused and preoccupied, and her inappropriate laughter returned. Her treatments were discontinued after the delivery, and little psychiatric improvement was noted at that time. She became withdrawn, preoccupied, and anxious, yet remained cognizant of the baby's existence. No emotional display in any direction was noticeable regarding the latter. A complete battery of psychological tests performed on Sept. 2 gave evidence of a long-standing schizophrenic illness with catatonic features.

By Sept. 6, 1954, the patient had improved sufficiently to go home with her husband on overnight visits. These visits were repeated on Sept. 11 and 19 and Oct. 3. She stayed home with her baby and husband from Oct. 16 through Oct. 21, and at that time she began to exhibit a pleasant frame of reference, remained in full contact, and was no longer confused. By Nov. 17 symptomatic remission had occurred, and during an interview on that day she fully realized that she had been extremely worried during her second pregnancy, fearing it might end in a complication similar to her previous delivery. She was fully aware of her own personality difficulties and her inadequacies, with which she had been struggling for as long as she could remember. She felt, however, that she was well enough to leave the institution and discharged herself, being a voluntary patient. She had fully accepted her baby. Recent follow-up reveals that she remains in good contact with reality, is very fond of the baby, and has not shown any overt psychotic behavior.

The baby boy was admitted to the pediatric service of Dr. Maxwell Borovsky at the Cook County Hospital for observation from Nov. 30 to Dec. 2, 1954, when he was a little over 3½ months old. He weighed 16 lb. (7,257 gm.). Examination revealed normal findings with respect to physical appearance, behavior, x-ray appearances of chest and the skeleton, and laboratory studies, including urinalysis, blood cell count, liver function tests, determination of nonprotein nitrogen content of the blood, and glucose tolerance test. The fasting blood sugar level was 87 mg. per 100 cc.; one hour after 100 cc. of 5% glucose by gavage, the blood sugar level was 139 mg. per 100 cc., after two hours, 91 mg. per 100 cc. At this writing, the baby is almost 6 months old and continues to be well and to develop normally.

COMMENT

It is now generally accepted that electroconvulsive therapy for mental illness can be safely administered throughout pregnancy. It would seem that insulin coma therapy begun in the latter half of pregnancy may be used without harm to the child and that pregnancy should not be considered a contraindication to needed shock therapy of this type. In the case reported, the 26th hour of insulin coma therapy was terminated only 13 hours before delivery, without ill-effects on mother or child.

ADDENDUM

Mother and child were reexamined by us on Oct. 11, 1955. The mother had remained well adjusted in her activities as a housewife and mother. Her husband reported that she was better than at any time he had known her, generally more friendly, sociable, and happy than before her illness. She displayed appropriate emotional response and was realistically aware that she had been seriously ill. The child, now 14 months old, showed normal physical and mental development. He weighed 30 lb. (13.6 kg.) and was 33 in. (83.8 cm.) tall. He had begun to walk at 10 months of age, now had a vocabulary of about 20 words, and was partially toilet trained.

29 E. Madison St. (2) (Dr. Luhan).

PROPANTHELINE (PRO-BANTHINE) BROMIDE IN RELATION TO NORMAL AND GLAUCOMATOUS EYES

EFFECTS ON INTRAOCULAR TENSION AND PUPILLARY SIZE

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and
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The increasing use of many autonomic blocking agents in various fields of medicine poses a hazard to the unwary patient with glaucoma or the person who may not realize he has glaucoma. Each new drug of clinical usefulness to the gastroenterologist, internist, and neurologist should receive ophthalmic evaluation in regard to both normal eyes and various types of glaucomatous eyes.

Our previous studies [1] with dicyclomine (Bentyl) hydrochloride showed single 10 mg. doses of this agent to have no effect on intraocular tension or pupillary size in a variety of nonglaucomatous patients hospitalized for other ophthalmic problems. In hospitalized glaucomatous patients with tensions reduced to the 19 to 32 mm. Hg (Schiøtz) range, however, such an orally given dose of dicyclomine hydrochloride was generally followed by a rise of 3 to 10 mm. Hg within one hour. This rise would continue to a peak within two to three hours, after which the tension would spontaneously return to the level before dicyclomine hydrochloride was administered in another two or three hours, or else a course of strong miotics would be required. These changes were without alteration in pupillary diameter. The purpose of the present study is to evaluate the effect of a single orally given dose of 15 mg. of propantheline

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The propantheline (Pro-Banthine) bromide used in this study was supplied by Mr. G. L. Standley of G. D. Searle & Co., Chicago.

1. Leopold, I. H., and others: Autonomic Ganglion and Parasympathomimetic Blocking Agents in Ophthalmology, read before the Fourth Wills Hospital Conference, Philadelphia, March 22, 1952.

(Pro-Banthine) bromide on intraocular tension and pupillary size in 20 successive glaucomatous patients and 20 nonglaucomatous control patients, without regard to age, color, or systemic disease.

PROCEDURE

Patients selected for study had known ophthalmic histories and were under the supervision of the eye clinic of the University of Louisville. The majority of them were in the older age groups. Intraocular tension and pupillary diameter were measured, and then the patient was given 15 mg. of propantheline bromide by mouth. Repeat measurements were made at one, two, and three hour intervals.

RESULTS

None of the 40 patients showed any significant alteration in pupillary diameter. Of the 20 normotensive control patients, none had significant elevations in tension. Two eyes showed an elevation of 3 mm. Hg at the one hour reading, and three eyes measured 2 mm. Hg higher at the end of three hours than on initial reading. Most eyes showed an average fall of 2 to 3 mm. Hg during the series of readings, probably on the basis of massage to the globe during previous measurements.

Of the 20 glaucomatous patients, 13 had chronic simple (open angle) glaucoma, one had primary chronic congestive glaucoma, and the remaining 6 had secondary glaucoma (2 secondary to uveitis; one secondary to traumatic intraocular hemorrhage; one secondary to posterior subluxation of the lens; and 2 secondary to cataract extraction with peripheral anterior synechia). Fifteen of these glaucomatous patients showed no significant rise in tension after the 15 mg. dose of propantheline bromide. Five eyes, however, showed increases of 6 to 14 mm. Hg apparent one hour after medication. Three of these eyes showed chronic simple (open angle) glaucoma with tensions that had been reduced under treatment to 40, 23, and 18.5 mm. Hg; their maximum increases amounted to 10, 6, and 11 mm. Hg respectively. One patient with glaucoma secondary to uveitis with a tension of 27 mm. Hg showed a rise of 11 mm. Hg, and the remaining patient, who had chronic congestive glaucoma with a tension of 22 mm. Hg, showed a rise of 14 mm. Hg. In general these increments were maintained at about the same level (average variation among successive readings on the same eye, 3.8 mm. Hg), and additional miotics were required to reduce the tension after these observations.

SUMMARY AND CONCLUSIONS

The effect of oral administration of 15 mg. of propantheline (Pro-Banthine) bromide on pupillary diameter and intraocular tension in the eyes of 20 glaucomatous patients and 20 control patients with normal eyes was quantitated. There was no effect on pupillary diameter in any eye and no significant alteration in intraocular tension in the eyes of the normotensive control patients. Five eyes in glaucomatous patients showed tension elevations of 6 to 14 mm. Hg that were generally sustained at the increased level during the three hour period of observation.

Propantheline bromide is a quaternary ammonium compound with anticholinergic or atropine-like actions similar to its antecedent, methantheline (Banthine) bromide, and older autonomic blocking agents such as dicyclomine (Bentyl) hydrochloride. Propantheline bromide appears to have no effect on the intraocular tension of nonglaucomatous eyes but may cause dangerous elevations of tension in eyes with either primary or secondary glaucoma. Patients who are to receive propantheline bromide treatment, particularly if they are above the age of 40, should have a preliminary tonometric evaluation of intraocular tension and a screening examination for glaucoma. The presence of glaucoma of any type is a relative contraindication to the use of propantheline bromide.

Heyburn Building (2) (Dr. Keeney).

OXYGEN FOR ACUTE RESPIRATORY DEPRESSION DUE TO ADMINISTRATION OF THIOPENTAL SODIUM

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and
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It is a well-recognized fact that barbiturates produce respiratory depression when administered intravenously, since their action as anesthetics is associated with depression of respiratory activity. For this reason it seemed worthwhile to compare the effects of thiopental (Pentothal) sodium on arterial blood oxygen of 18 patients undergoing a simple surgical procedure with the effects of administering oxygen simultaneously with the thiopental sodium to another group of 10 patients. In this group of 28 female patients, between the ages of 19 and 37, all had a diagnosis of incomplete abortion and were brought to surgery for a therapeutic dilation and curettage. Except for the presence of mild to severe anemias there were no other complicating medical conditions.

PROCEDURE

All patients were given 1/150 grain (0.4 mg.) of atropine as premedication one hour before surgery. Under local anesthesia a Cournand needle was placed in either the radial or brachial artery. There were no complications in any patient due to an indwelling intra-arterial needle. After several moments to allow for acclimation, an arterial blood sample was drawn, from which duplicate oxygen determinations were made by the Van Slyke-Neil technique. The hemoglobin level was determined with an accurately calibrated colorimetric hemoglobinometer. It was planned initially to use atropine premedication and thiopental sodium alone for these studies, but reactions of the patients were such that this procedure was considered unsafe. Consequently, the procedure was modified, and 100 mg. of meperidine (Demerol) hydrochloride diluted to 10 cc. was slowly injected intravenously. Five minutes after

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the injection was made, an arterial blood sample was drawn and an oxygen analysis made. In several patients, not included in this series, arterial blood samples were drawn at 10 and 15 minute intervals after the injection to determine the effect of meperidine hydrochloride alone upon arterial oxygen content. After the withdrawal of the arterial blood sample, made after administration of meperidine hydrochloride, thiopental sodium was administered intravenously in amounts just adequate to completely obtund reflex reaction to perineal stimulation in an effort to establish as consistent an anesthetic endpoint as possible. Five minutes after the injection of thiopental sodium another arterial blood sample was taken. Nitrous oxide and oxygen were then administered in a 3:1 ratio with slightly assisted respiration for 10 minutes and a final arterial blood sample withdrawn. In the second series consisting of 10 patients the procedure was modified only to the extent that pure oxygen was administered by a mask for five minutes before the initial injection of meperidine hydrochloride and thereafter during the entire procedure until the course with nitrous oxide and oxygen mixture was started.

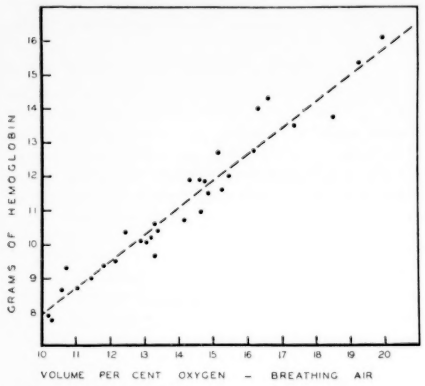

Fig. 1.—Relationship observed between volume per cent of oxygen and arterial blood and the hemoglobin level in patients who are awake and breathing room air.

RESULTS

Figure 1 shows the relationship that was observed between volume per cent of oxygen and arterial blood and the hemoglobin levels in these patients who were awake and breathing room air. It was interesting to note that in the majority of these patients the hemoglobin level values were less than 13 gm. per 100 cc. and the oxygen content of the arterial blood less than 16 vol. %. Moderate anemia is a common clinical finding, and its importance should be carefully considered in the administration of clinical anesthesia. The hemoglobin content of the blood was recognized as a measurable variable in this series. However, resting arterial oxygen saturations of these patients breathing air were within normal limits in all cases (90% and 95% saturated), and, therefore, this variable was not considered to be significant in these studies.

FIRST SERIES

The first series was comprised of 18 patients who had had simple surgical procedures.

Effects of Intravenously Administered Meperidine Hydrochloride.—The intravenous injection of 100 mg. of a dilute solution of meperidine hydrochloride produced no untoward effect in any patient. The maximum respiratory depression was found to occur about five minutes after the intravenous administration of morphine or after respiration. All patients experienced drowsiness, lassitude, and a feeling of well-being at the end of the five minute period. Figure 2 shows the effects of 100 mg. of intravenously given meperidine hydrochloride on the arterial oxygen content of these 18 patients. The average drop in arterial oxygen from the resting level was approximately 2.5%. It should be noted, however, that the reaction was variable, and in one patient the drop was 12%.

Effect of Thiopental Sodium.—The intravenous injection of thiopental sodium produced a drop in arterial oxygen, as was expected. The combined depressant action of meperidine hydrochloride and thiopental sodium lowered the arterial oxygen content to an average of 10% below the level of these patients awake and breathing room air. Since no relationship could be established between the effects of the intravenous administration of meperidine hydrochloride and the effects of thiopental sodium on the drop in arterial blood oxygen content, it was not considered necessary or desirable to relate each individual procedure with a line graph. It was felt that the trend and general principle noted in this series of observations was of more importance than the individual reactions, which were highly variable.

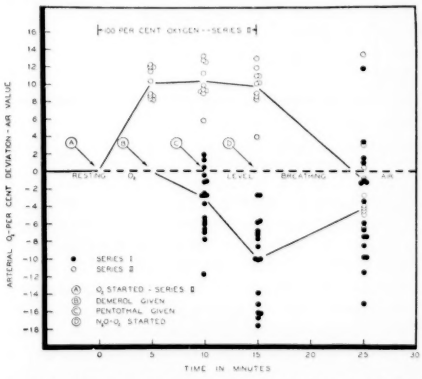

Fig. 2.—Mean arterial oxygen level remains unchanged at a value of 10% above that of resting level when patients who are breathing pure oxygen receive meperidine (Demerol) hydrochloride intravenously.

Effect of the Addition of Nitrous Oxide and Oxygen.—There was a tendency for the oxygen content of the arterial blood to return to the meperidine hydrochloride

level after the administration of 25% oxygen and 75% nitrous oxide, although the patients were in essentially the same level of anesthesia from all objective signs. The spread in the arterial content of the blood, however, was wide, and it is our belief that the grouping would have been better if a similar study could have been done with nitrous oxide and oxygen substituted for the oxygen, as in series 2. Nevertheless, it is felt that nitrous oxide and oxygen are justified and indicated in lessening the over-all respiratory depression to the level observed when thiopental sodium alone is administered.

SECOND SERIES

In the second series, comprised of 10 patients, the procedure was modified, in that pure oxygen was administered.

Effect of Breathing Pure Oxygen.—In series 2 of figure 2 a significant average increase of 10% in arterial oxygen content is shown when pure oxygen is substituted for room air. This group showed surprisingly little

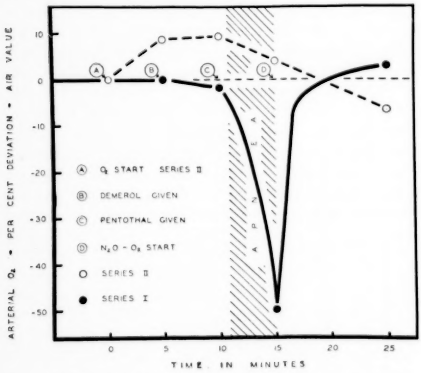

Fig. 3.—Fall in arterial oxygen content when apnea occurred in one patient after administration of thiopental (Pentothal) sodium.

variability, and the findings are roughly consistent with the theoretical amount of oxygen taken up in solution by the plasma due to an increase of partial pressure of oxygen from 100 to 600 mm. Hg.

Effect of Intravenous Administration of Meperidine Hydrochloride.—When patients who are breathing pure oxygen receive intravenous administration of meperidine hydrochloride, the mean arterial oxygen level remains unchanged at a value of 10% above that of resting level (fig. 2). It is thought to be significant not only in relation to anesthesia but to general patient care; that intravenously given meperidine hydrochloride, which produces a small but significant drop in arterial oxygen in patients breathing room air, fails to do so in patients breathing a high concentration of oxygen. It seems that this has implications applicable to the care of patients in the immediate postoperative period when drugs used as premedication and as anesthetics may still be exerting a depressant effect.

Effect of Thiopental Sodium.—In this group of patients breathing pure oxygen instead of room air, the combined action of meperidine hydrochloride and thiopental sodium produced no significant drop in arterial oxygen content. The oxygen content continued at a higher level than the resting normal value despite the fact that apnea of several minutes was not uncommon after the injection of thiopental sodium. Such protection against hypoxia seems significant, especially during induction of anesthesia and during endotracheal intubation.

Effect of Addition of Nitrous Oxide and Oxygen.—The lowering of the arterial oxygen level to that of the effects of intravenously administered meperidine hydrochloride reaffirms the effect of that medicament alone on respiratory activity and, we believe, demonstrates that the supplementation of thiopental sodium anesthesia with nitrous oxide and oxygen is justified and indicated.

EFFECT OF APNEA ON ARTERIAL OXYGEN CONTENT

One of the patients, not included in this series, showed apnea after administration of thiopental sodium (fig. 3). Four minutes later controlled respiration with 75% nitrous oxide and 25% oxygen was instituted. The patient was dark skinned, and cyanosis was not observed; however, the fall in arterial oxygen content was severe, particularly when contrasted with the stable oxygen level found in another patient breathing pure oxygen, who was also in apnea for the same period of time following the administration of thiopental sodium. We feel that these two cases illustrate dramatically the dangers inherent in thiopental sodium anesthesia and serve to emphasize the importance of giving a high concentration of oxygen with thiopental sodium, especially during the induction period.

SUMMARY AND CONCLUSIONS

It is possible to materially increase a patient's arterial oxygen content by administering pure oxygen during the induction of thiopental (Pentothal) sodium anesthesia. In the case of a person with moderate to severe anemia this may prevent a dangerous period of hypoxia, especially if apnea occurs without adequate assisted respiration. We feel that these findings constitute a strong argument against the promiscuous use of thiopental sodium without oxygen for even short periods and that the arterial oxygen content of patients breathing 25% oxygen and 75% nitrous oxide argues for its routine employment during maintenance of anesthesia. We have, as a direct result of this investigation, adopted a policy of giving patients pure oxygen for five minutes before endoscopy when thiopental sodium is used for induction of anesthesia. We believe that the evidence presented in these studies indicates that a brief period of safe apnea is thus assured for examinations or manipulations of short durations. A similar routine is followed for patients with endotracheal intubation, thus providing an extra margin of safety for the occasional difficult intubation.

COMMITTEE ON COSMETICS

Report to the Committee

The following report on acne vulgaris has been prepared at the request of the Committee.

VERONICA LUCEY CONLEY, *Secretary*

ACNE VULGARIS

Frederick D. Malkinson, M.D., Chicago

Acne vulgaris in mild form is so common in adolescent males and females that it can almost be regarded as a physiological alteration associated with other puberal changes. However, largely because of modern society's undue emphasis on the individual's personal appearance, the more serious forms of acne represent a true disease, which, though seldom endangering health, is not to be lightly dismissed because of its disturbing psychological, social, and economic consequences. The latter problems arise from the general population's latent antipathy to skin disfigurements and the subsequent deleterious mental effects engendered in certain patients. Many patients are tormented by feelings of abnormality and inferiority and shun all but essential social contacts. Girls are deprived of social engagements, young men are rejected for employment, and obstacles to marriage in either sex may be considerable. The degree of mental reaction is, of course, an individual variant, but not infrequently it is of sufficient severity to produce serious depression, withdrawal, and, occasionally, even expression of suicidal thoughts. Furthermore, interviews with unafflicted members of the adult population reveal that many associate acne with disturbed general health, "social disease," and irregular sexual practices.[1] The inexorable correlation of skin disease with dirt persists, as does the inescapable suspicion of contagiousness. It is little wonder then that the patient's suffering is derived more from the condemnation of a complexion-conscious society than from the symptomatology of his disease. The importance of therapy to all who seek it is apparent, and the intelligent approach combines reassurance and encouragement with treatment methods reflecting cognizance of the pathophysiology of the disease.

The association of acne lesions with the pilosebaceous unit was recognized over 200 years ago.[2] It is well known today that there are two main pathogenic factors: hyperplasia of sebaceous glands with subsequent seborrhea and hyperkeratinization of the follicular pore. The first development, and perhaps the second, is produced by the physiologically increased testosterone levels in boys and increased progesterone levels in girls at puberty.[3] The severity of response of the target organ, the pilosebaceous apparatus, is apparently determined by genetic factors. Where hyperkeratosis at the follicular opening causes blockage of the sebum exit there is dilatation of the follicle. Stagnation and decomposition of sebum is followed by perifollicular inflammation and often by secondary bacterial infection. Pressure of the macroscopic or microscopic comedo resulting in fragmentation of the follicular wall and sebaceous gland may produce atrophy.[4] The clinical progression of acne lesions through the stages of comedo, papule, pustule, and cyst reflects the sequence of these pathological changes, while the occurrence of pitted scarring depends on the degree of destruction of the pilosebaceous apparatus and perifollicular connective tissue.

It is known that testosterone in the male and progesterone in the female are prerequisites for the development of acne. Furthermore, animal experiments have shown that these effects are counteracted by administration of large amounts of estrogenic hormone. Nevertheless, a practical approach to hormonal treatment of acne is still lacking because the high dosage of estrogens required to produce clear-cut reduction in sebaceous gland volume [5] is rendered impractical for clinical usage by the accompanying dangerous side-effects in both sexes. At present, then, treatment depends rather on utilization of empirically established local and general measures that vary in scope and intensity with the severity of skin changes.

LOCAL THERAPY

Local therapy is essentially directed toward combating sebaceous gland hyperplasia and seborrhea and toward eradicating keratin plugs, thereby preventing development of new lesions. Sulfur, which has a pronounced antiseborrheic effect, and keratolytics such as strong alkaline soaps, resorcinol, and salicylic acid are principal agents employed to achieve these objectives. Using hot water and soap, the patient gently massages the skin of the face between the fingers for 5 to 10 minutes each night. (Personal experience indicates that potassium soap [medicinal soft soap, U. S. P.] is more effective than the conventional sodium soaps.) After rinsing with cool water and blotting the skin dry with a towel, a lotion or paste containing one or more antiseborrheic and keratolytic substances is applied. Such preparations must be test-applied initially to a limited skin area to avoid widespread irritation. It is safest to begin with nightly application of a shake-type lotion composed of: precipitated sulfur, 3 gm.; resorcinol, 2 gm.; zinc oxide, 22.5 gm.; talc, 22.5 gm.; glycerin, 10 gm.; and purified water sufficient to make 100 cc.

If such a lotion can be tolerated, the strength of the active ingredients may be gradually increased to maintain dryness and slight scaling. Concentrations to 20% sulfur and 5% resorcinol in the above vehicle can be

From the Section of Dermatology, Department of Medicine, University of Chicago.

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3. Hamilton, J. B.: Male Hormone Substance: A Prime Factor in Acne, J. Clin. Endocrinol. **1**: 570 (July) 1941. Haskin, D.; Lasher, N., and Rothman, S.: Some Effects of ACTH, Cortisone, Progesterone and Testosterone on Sebaceous Glands in the White Rat, J. Invest. Dermat. **20**: 207 (March) 1953.
4. Lynch, F. W.: Acne Vulgaris: Review of Histologic Changes Observed in Early Lesions, Arch. Dermat. & Syph. **42**: 593 (Oct.) 1940.
5. Ebling, F. J.: Sebaceous Glands: The Effect of Sex Hormones on the Sebaceous Glands of the Female Albino Rat, J. Endocrinol. **5**: 297 (June) 1948.

used. For severe cystic forms of acne, the following freshly prepared sulfurated lime solution (Vleminckx' solution), a strong sulfide preparation, is especially useful: sulfurated lime solution, 8 cc., 10 cc., or 12 cc., and purified water sufficient to make 120 cc.

Ideally, all local applications to acne areas should be free of greases for reasons that are readily apparent. On the other hand it is well known that the effects of sulfur and salicylic acid are potentiated if applied after incorporation into pastes and ointments. The advantages of this enhanced action are obvious when the concentrations of antiseborrheic and keratolytic agents are high. Accordingly, the following paste may be used when clinical response to lotions is inadequate: precipitated sulfur, 10 gm.; salicylic acid, 5 gm.; resorcinol, 2 gm.; and zinc oxide ointment, U. S. P., sufficient to make 100 gm.

Although excellent results have been obtained with such a paste, some dermatologists prefer to avoid all greasy or pasty bases, using instead emulsion bases or water-washable vehicles with sulfur, such as described

Lotion with Coloring Material for Daytime Use

	Light	Medium	Dark
Neutracolor	2.9 gm.	4.2 gm.	6.7 gm.
Zinc oxide	.....	8.3 gm.	.....
Talc	.....	8.3 gm.	.....
Calamine	.....	8.3 gm.	.....
Glycerin	.....	8.3 gm.	.....
Alcohol 70%	.....	16.6 cc.	.....
Purified water sufficient to make	.....	100.0 cc.	.....
May add			
Precipitated sulfur	3%	5%	10%
Resorcinol	2%	2%	2%

by Frazier and Blank.[6] For daytime applications a lotion with admixture of coloring materials designed to approximate skin color can be used (see table). Daytime use of this type of lotion provides the advantages of more continuous therapy.

It is hardly necessary to mention that numerous commercially compounded preparations containing sulfur, resorcinol, and so forth are readily available. Although such preparations are not in themselves objectionable, the experienced physician prefers magistral prescriptions that allow him full freedom in selecting the vehicles and concentrations of active ingredients best suited to the individual case.

ULTRAVIOLET AND X-RAY THERAPY

Summertime improvement in patients with all forms of acne attests to the beneficial hyperemic and desquamative effects of ultraviolet light. While fairly intense ultraviolet radiation with mercury vapor lamps can be given as an office procedure, satisfactory results may be obtained from the home use of a small inexpensive bulb (RS model) that inserts into a standard lamp socket. At a distance of 15 in., irradiation of affected parts is begun with an exposure time of one minute; this is increased by 30 seconds each day until a 10 minute exposure time is reached. Such treatment is then continued daily at the same time level. For irradiation of the face, the left side, right side, and front are successively exposed after the eyes are protected with moist cotton. Directions concerning protection of untreated areas and precautions against overexposure are essential. A careful balance between the use of local applications and ultraviolet rays is necessary to avoid excessive drying, erythema, and scaling.

Judiciously administered x-ray therapy may be of great value in severe cases. Selection of patients and technique of administration, however, must be left to those with specialized training. The work of Sulzberger and his associates [7] has shown that in expert hands this treatment method does not involve harmful sequelae.

GENERAL MEASURES

In addition to therapy of affected parts, care of the scalp is important. Acne lesions here are rare, but correction of seborrhea and excessive scaling of the scalp, when present, seems to be beneficial to facial acne. Shampoos with medicinal soft soap liniment, U. S. P. (tincture of green soap), can be given twice weekly, followed by an ointment containing an average concentration of 3% sulfur and 2% salicylic acid in rose water ointment, U. S. P. The use of a cold cream base facilitates effective massage. Again, some dermatologists prefer emulsion bases or water-washable vehicles for such treatment.

Certain additional measures are indicated. Female patients should avoid cosmetic preparations with greasy bases; for males, omission of hair pomades is desirable and short haircuts facilitate scalp care. To avoid self-inflicted scar formation and spread of infection, all patients must refrain from squeezing blackheads, pustules, and cysts.

Occasionally, local procedures in the office are helpful. While cysts are best treated conservatively with hot compresses, persistent fluctuation without signs of involution may require active drainage. With the patient under ethyl chloride anesthesia, fluctuant lesions can be aspirated with a large-bore needle or incised with a small opening at the dependent portion.

Since topical applications eliminate most comedones, manual extraction of these lesions is seldom necessary. When results of treatment are limited and comedones numerous or deeply imbedded, hot compresses locally followed by careful removal with a comedo extractor, without application of undue pressure, may be desirable. Also often helpful in cases of pustular, nodular, and cystic acne, is the local use of carbon dioxide "slush," a mixture containing dry ice and acetone, with or without sulfur. This preparation, applied with the gauze-wrapped tip of a tongue depressor, may be used once or twice weekly and produces a satisfactory postinflammatory exfoliation.

6. Frazier, C. N., and Blank, I. H.: A Formulary for External Therapy of the Skin, Publication 201, American Lecture Series, Monograph in American Lectures in Dermatology, Springfield, Ill., Charles C Thomas, Publisher, 1954, p. 94.

7. Sulzberger, M. B.; Baer, R. L., and Borota, A.: Do Roentgen-Ray Treatments as Given by Skin Specialists Produce Cancers or Other Sequelae? Follow-Up Study of Dermatologic Patients Treated with Low-Voltage Roentgen Rays, A. M. A. Arch. Dermat. & Syph. **65**: 639 (June) 1952.

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General measures are recommended in the treatment of almost every patient with acne vulgaris. The efficacy of some of these measures varies considerably in individual cases, however, as do practitioners' estimations of their value. The initial recommendations are those most observers might consider useful.

The relationship of diet to all forms of acne has long been appreciated, and certain restrictions are advisable. Apparently some foods may produce aggravation either by increasing sebum production or by producing follicular irritation. Representative of the former group are carbohydrates and fats, while nuts, chocolate, and strong cheeses are representative of the latter group. For this reason, the intake of those foods should be reduced. Since iodides and bromides may produce acneform eruptions via follicular irritation, seafood and shellfish should be proscribed and in severe cases use of noniodized salt should be recommended. All patients must be warned against taking iodide or bromide medicaments. Dietary restrictions with compensatory increase in protein intake may be imposed initially on every patient, but continued rigid adherence may be unnecessary. Since many patients respond satisfactorily to local therapy despite the nature of their diets, it is apparent that dietary therapy must be individualized.

In cases of pustular and cystic acne antibiotic therapy has often been administered systemically. Long-acting penicillin preparations for intramuscular use [8] or 0.5 to 2 gm. of chlortetracycline or oxytetracycline for oral use daily [9] can be given until the active infection is optimally controlled, although repeated courses are often required. While the pustular element often improves remarkably, lack of uniform response, frequent side-effects, and expense of medication limit the practicability of such treatment. Local use of antibiotic ointments is of doubtful value.

Experience with so-called tropical acne among the troops in the South Pacific during the last war demonstrated that a hot, humid environment fosters development of acneform lesions, presumably by stimulating follicular hyperkeratosis and blocking pores.[10] Where similar factors exist, a drier climate may be beneficial to the patient with advanced acne.

HORMONES, VITAMIN A, AND TOXOIDS OR VACCINES

There remain for brief discussion such controversial remedies as hormone preparations, vitamin A, and toxoids or vaccines. As mentioned previously, the pathophysiology of acne vulgaris suggests therapeutic possibilities in the use of estrogens to overcome progesterone and testosterone effects. Systemic administration of diethylstilbestrol, conjugated estrogenic substances, or chlorotrianisene [11] has been widely recommended and done with varying dosages, being restricted to patients 18 years of age or older and, in the female, to the latter half of the ovulatory cycle. Side-effects include nausea and menstrual disturbances and, in the male, gynecomastia and loss of libido. The effectiveness of such therapy in dosages safe to administer remains debatable, and estrogens are therefore indicated only in extreme cases resistant to all other methods of treatment. Local application of these hormones to avoid systemic effects has produced inconclusive results, but, because of the remarkable absorption of steroids from the skin surface, strict dosage regulation is still required.

The use of Micrococcus (Staphylococcus) toxoids [12] and autogenous and stock vaccines followed the presumption that bacterial infection of acne lesions was an important pathogenic factor. Results from such preparations are sometimes surprisingly good when cysts and papules predominate. Whether the beneficial effect results from a desensitization process or merely reflects foreign protein therapy is problematical. The material is given intracutaneously in graduated dosages once or twice weekly for 10 to 20 injections. Such a course of treatment may be repeated after a four to six week interval.

Vitamin A preparations [13] also have their proponents. This substance, in sufficiently high dosages, interferes with follicular plug formation by virtue of its antikeratinizing potency. Water-miscible vitamin A preparations have been administered orally in dosages up to 100,000 units daily for periods of several months and have been claimed to be beneficial. In most cases, however, this method of therapy has been disappointing.

In occasional recalcitrant cases characterized by deep infiltrates and cyst formation, hospitalization of the patient for administration of fever therapy by any mode may be a very effective aid to treatment.

The recent introduction of surgical skin-planing techniques,[14] while still in a developmental phase, holds promise in the important field of improving unsightly scarring once disease activity has subsided. Only the experienced dermatologist or plastic surgeon should perform this procedure.

SUMMARY

In summary, most patients respond satisfactorily to the described local measures, together with ultraviolet light therapy and possibly dietary restrictions. In certain severe cases, discerning use of x-ray therapy, antibiotics, vaccines, fever therapy, and perhaps estrogens may improve results. In severe nodular and cystic cases, however, the present therapeutic armamentarium does not always yield satisfactory results, and the need for further clinical research in this field is readily apparent.

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11. Sulzberger, M. B., and Witten, V. H.: Symposium on Diseases of the Skin: Hormones and Acne Vulgaris, M. Clin. North America **35**: 373 (March) 1951. Welsh, A. L.: Use of Synthetic Estrogenic Substance Chlorotrianisene (TACE) in Treatment of Acne, A. M. A. Arch. Dermat. & Syph. **69**: 418 (April) 1954.

12. MacDonald, T. C., and Taylor, F.: Staphylococcus Toxoid and Pustular Acne, Lancet **2**: 558 (Sept. 29) 1951.

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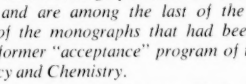
CHEMICAL LABORATORY

TESTS AND STANDARDS FOR NONOFFICIAL DRUGS

The following monographs were developed by the Chemical Laboratory for drugs that had been evaluated prior to Jan. 1, 1955, by the Council on Pharmacy and Chemistry. These monographs have not been published previously and are among the last of the Tests and Standards of the monographs that had been prepared during the former "acceptance" program of the Council on Pharmacy and Chemistry.

WALTER WOLMAN, Ph.D., *Director.*

Acetyl Sulfisoxazole.—$C_{13}H_{15}N_3O_4S$.—M.W. 309.35. —N^1-(Acetyl-3,4-dimethyl-5-isoxazolyl)sulfanilamide. —The structural formula of acetyl sulfisoxazole may be represented as follows:



Physical Properties: Acetyl sulfisoxazole is a white to slightly off-white, crystalline solid, with a slight characteristic odor. It melts at 192-195°. It is practically insoluble in water. The approximate amounts that dissolve at 25° in the following solvents to form 100 ml. of solution are: 0.4 gm. in alcohol, 2 gm. in chloroform, and 0.2 gm. in ether.

Identity Tests: Dissolve about 10 mg. of acetyl sulfisoxazole in about 1 ml. of hydrochloric acid and add 9 ml. of water. Cool the solution in an ice bath and add 3 drops of 1% sodium nitrite solution and 1 ml. of 10% sodium hydroxide containing 10 mg. of β-naphthol: an orange precipitate forms (*presence of a primary amino group*).

Prepare a 0.001% solution of acetyl sulfisoxazole as follows. Transfer to a 100 ml. volumetric flask 0.1 gm. of acetyl sulfisoxazole, accurately weighed, fill to the mark with alcohol, and mix. Transfer to a second 100 ml. volumetric flask 10 ml. of this solution, fill to the mark with alcohol, and mix. Finally transfer to a third 100 ml. volumetric flask 10 ml. of this last solution, fill to the mark with alcohol, and mix. This solution exhibits ultraviolet absorbance maxima at 220 and 292 mμ, and a minimum at 248 mμ.

Purity Tests: Make the following solutions. Prepare 0.1% Bratton-Marshall reagent by dissolving 0.1 gm. of N-(1-naphthyl) ethylenediamine dihydrochloride in water and diluting to 100 ml. in an amber glass volumetric flask. This solution is stable for 4 weeks when kept cold. Prepare 0.1% sodium nitrite and 0.5% ammonium sulfamate (stable for 4 weeks when kept cold in an amber bottle) and keep in the cold. Transfer to a 1,000 ml. volumetric flask 0.5 gm. of sulfisoxazole, U. S. P., accurately weighed, and dissolve it in 50 ml. of 0.1 *N* sodium hydroxide, using heat if necessary. Cool to room temperature, fill to the mark with water, and mix. Transfer to a 100 ml. volumetric flask 10 ml. of this solution, fill to the mark with water, and mix (Standard Solution). Transfer to a 100 ml. volumetric flask 0.2 gm. of acetyl sulfisoxazole, accurately weighed, add 2 ml. of saturated sodium bicarbonate solution, and shake for 5 min. Fill to the mark with water, mix, and allow the suspended material to settle. Transfer to a 120 ml. separatory funnel 50 ml. of the solution, accurately measured, extract with five 10 ml. portions of benzene, and discard the benzene. Transfer to a 50 ml. beaker 20 ml. of the extracted solution, accurately measured, and warm on a steam bath in a current of air to remove the residual benzene. Cool to room temperature, with the aid of small portions of water completely transfer the solution to a 50 ml. volumetric flask, fill to the mark with water, and mix (Sample Solution). In one 25 ml. volumetric flask place 15 ml. of water (Blank), in another 5 ml. of Standard Solution and 10 ml. of water, and in a third 15 ml. of Sample Solution. To each flask add 1 ml. of 4 *N* sulfuric acid and 1 ml. of 0.1% sodium nitrite. Stopper the flasks, shake well, and let stand for 5 min. Add 1 ml. of 0.5% ammonium sulfamate, stopper the flasks, shake well, and let stand for 2 min. Add 1 ml. of 0.1% Bratton-Marshall reagent, stopper the flasks, shake well, dilute to the marks with water, and mix. Allow the color to develop for 15 min. in the dark. Spectrophotometrically determine the absorbancy in 1 cm. cells at 540 mμ, using the prepared Blank Solution to set the instrument. The concentration of sulfisoxazole in mg./ml.=(absorbance÷absorbance of the standards)× concentration of sulfisoxazole in the standard. The amount of nonacetylated sulfisoxazole present in acetyl sulfisoxazole is not more than 2.5%.

Dry about 1 gm. of acetyl sulfisoxazole, accurately weighed, at 105° for 4 hours: the loss in weight does not exceed 0.5%.

Char about 1 gm. of acetyl sulfisoxazole, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.1%. Save the residue for a heavy metals determination.

Dissolve the residue from the sulfated ash determination in 23 ml. of water, add 2 ml. of diluted acetic acid, and run a *U. S. P. heavy metals test:* the amount of heavy metals does not exceed 20 ppm.

Assay: (Acetyl Sulfisoxazole) Standardize a solution of 0.1 *N* sodium nitrite as follows. Transfer to a 250 ml. beaker 0.5 gm., accurately weighed, of U. S. P. reference standard sulfanilamide, previously dried for 3 hours at 105°. Dissolve it in 25 ml. of hydrochloric acid with warming, if necessary. Add 15 ml. of glacial acetic acid and 100 ml. of water, and cool to room temperature. Titrate potentiometrically using a calomel and a platinum electrode. The normality of the sodium nitrite= gm. sulfanilamide÷172.2. Transfer to a 250 ml. beaker 1.0 gm. of acetyl sulfisoxazole, accurately weighed, and dissolve it in 25 ml. of hydrochloric acid without warming. Add 15 ml. of glacial acetic acid and 100 ml. of water, and cool to room temperature. Titrate potentiometrically with 0.1 *N* sodium nitrite, using a calomel and a platinum electrode. Each milliliter of 0.1 *N* sodium nitrite is equivalent to 0.03094 gm. of anhydrous acetyl sulfisoxazole. The amount of acetyl sulfisoxazole is not less than 97.0 nor more than 103.0%.

Dosage Forms of Acetyl Sulfisoxazole

SUSPENSION. *Identity Tests:* Transfer to a 125 ml. separatory funnel an amount of suspension equivalent to about 0.5 gm. of acetyl sulfisoxazole, and add 10 ml. of sodium hydroxide T. S. and 90 ml. of water. Extract this solution with four 15 ml. portions of chloroform. Filter the chloroform extracts through a pledget of cotton and evaporate the filtrate on a steam bath in a current of air. The residue responds to the identity tests for the active ingredient in the monograph for acetyl sulfisoxazole.

Assay: (Acetyl Sulfisoxazole) Using a pipet "to contain," transfer to a 250 ml. beaker an amount of suspension, accurately measured, equivalent to about 1 gm. of acetyl sulfisoxazole. Wash the pipet with a few small portions of water and add 25 ml. of hydrochloric acid to dissolve the acetyl sulfisoxazole, using heat if necessary. Add 15 ml. of glacial acetic acid and enough water to give a total volume of about 140 ml. Cool to room temperature. Titrate potentiometrically with 0.1 *N* sodium nitrite (standardized potentiometrically), using a calomel and a platinum electrode. Each milliliter of 0.1 *N* sodium nitrite is equivalent to 0.03094 gm. of anhydrous acetyl sulfisoxazole. The amount of acetyl sulfisoxazole is not less than 93.0 nor more than 107.0% of the labeled amount.

SYRUP. *Identity Tests:* Transfer to a 125 ml. separatory funnel an amount of syrup equivalent to about 0.5 gm. of acetyl sulfisoxazole, and add 10 ml. of sodium hydroxide T. S. and 90 ml. of water. Extract this solution with five 15 ml. portions of chloroform. If necessary, centrifuge for a few minutes at 2,500 rpm to separate completely the chloroform layer. Evaporate the chloroform on a steam bath in a current of air. The residue responds to the identity tests for the active ingredient in the monograph for acetyl sulfisoxazole.

V 1
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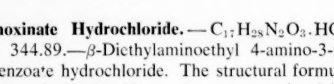
Assay: (Acetyl Sulfisoxazole) Using a pipet "to contain," transfer to a 250 ml. beaker an amount of syrup, accurately measured, equivalent to about 1 gm. of acetyl sulfisoxazole. Wash the pipet with a few small portions of water and add 25 ml. of hydrochloric acid to dissolve the acetyl sulfisoxazole, using heat if necessary. Add 15 ml. of glacial acetic acid and enough water to give a total volume of about 140 ml. Cool to room temperature. Titrate potentiometrically with 0.1 *N* sodium nitrite (standardized potentiometrically), using a calomel and a platinum electrode. Each milliliter of 0.1 *N* sodium nitrite is equivalent to 0.03094 gm. of anhydrous acetyl sulfisoxazole. The amount of acetyl sulfisoxazole is not less than 93.0 nor more than 107.0% of the labeled amount.

Hoffmann-La Roche, Inc., cooperated by furnishing scientific data to aid in developing this monograph.

Benoxinate Hydrochloride. — $C_{17}H_{28}N_2O_3 \cdot HCl$. — M.W. 344.89.—β-Diethylaminoethyl 4-amino-3-n-butoxybenzoate hydrochloride. The structural formula of benoxinate hydrochloride may be represented as follows:



Physical Properties: Benoxinate hydrochloride is a white, odorless, crystalline powder. It melts at 157-160°. It is freely soluble in alcohol, chloroform, and water but insoluble in ether. Benoxinate hydrochloride is stable to air, heat, and light. The pH of a 1% solution is 4.0-5.2.

Identity Tests: Dissolve about 0.1 gm. of benoxinate hydrochloride in 10 ml. of water. To 5 ml. of this solution add 1 ml. of silver nitrate T. S.: a white precipitate forms, which is insoluble in nitric acid but soluble in a slight excess of ammonia T. S. (*presence of chloride*). To the second 5 ml. portion of the solution add 0.5 ml. of diluted hydrochloric acid and 0.5 ml. of 10% sodium nitrite, followed by 10 ml. of diluted ammonia solution containing 0.2 gm. of β-naphthol: a red precipitate forms (*presence of a primary aromatic amine*).

Dissolve 0.1 gm. of benoxinate hydrochloride in 10 ml. of water and add sodium hydroxide T. S.: the solution turns milky white and, on standing, drops of oil collect.

Dissolve about 0.2 gm. of benoxinate hydrochloride in 15 ml. of water and add 2.5 ml. of 25% potassium thiocyanate. Allow the milky solution to stand in the cold until precipitation is complete. Filter the mixture, dissolve the residue in the least possible amount of hot water, and allow to crystallize in the cold. Filter the crystals and dry in a vacuum desiccator over phosphorus pentoxide for about 5 hours. The substance melts at 102-105°.

A 0.001% solution, prepared as directed in the spectrophotometric assay for benoxinate hydrochloride, exhibits an ultraviolet absorbance maximum at about 308 mμ [absorptivity (1%, 1 cm.), about 426].

Purity Tests: Dry about 1 gm. of benoxinate hydrochloride, accurately weighed, at 105° for 3 hours: the loss in weight does not exceed 0.5%.

Ignite about 1 gm. of benoxinate hydrochloride, accurately weighed: the residue does not exceed 0.5%.

Assay: (Benoxinate Hydrochloride) Prepare a 0.001% solution of benoxinate hydrochloride as follows. Transfer to a 100 ml. volumetric flask 0.1 gm. of benoxinate hydrochloride, accurately weighed, fill to the mark with water, and mix. Transfer to a second 100 ml. volumetric flask 1 ml. of this solution, fill to the mark with water, and mix. Spectrophotometrically determine the absorbance in a 1 cm. quartz cell at 308 mμ, using water as a blank. The concentration of anhydrous benoxinate hydrochloride in the solution in mg./ml.=absorbance÷42.6. The amount of benoxinate hydrochloride is not less than 95.0 nor more than 105.0%.

(Benoxinate) Transfer to a 60 ml. separatory funnel about 0.2 gm. of benoxinate hydrochloride, accurately weighed. Add 15 ml. of water and 3 ml. of ammonium hydroxide, and extract the liberated base with five 15 ml. portions of ether. Wash the combined ether extracts with 10 ml. of water, extract the water with 10 ml. of ether, and add the ether to the main extract. Evaporate the ether in a stream of air to about 10 ml. Add exactly 20 ml. of 0.1 *N* sulfuric acid, stir well, and heat gently until all the ether is expelled. Cool and titrate the excess acid with 0.1 *N* sodium hydroxide, using methyl red T. S. as an indicator. Each milliliter of 0.1 *N* sulfuric acid consumed is equivalent to 0.03084 gm. of benoxinate and 0.03449 gm. of anhydrous benoxinate hydrochloride. The amount of benoxinate is not less than 85.0 nor more than 93.9%, equivalent to not less than 95.0 nor more than 105.0% of benoxinate hydrochloride.

Dosage Forms of Benoxinate Hydrochloride

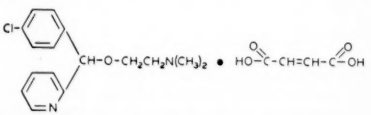
SOLUTIONS. *Physical Properties:* The pH of the solution is 4.0-5.2.

Identity Tests: The solution responds to the identity tests for the active ingredient in the monograph for benoxinate hydrochloride.

Assay: (Benoxinate Hydrochloride) Transfer to a 1,000 ml. volumetric flask an amount of solution, accurately measured, equivalent to about 8 mg. of benoxinate hydrochloride. Fill to the mark with water and mix. Spectrophotometrically determine the absorbance of the solution in a 1 cm. quartz cell at 308 mμ, using water as a blank. The concentration of anhydrous benoxinate hydrochloride in the solution in mg./ml.=absorbance÷42.6. The amount of benoxinate hydrochloride is not less than 95.0 nor more than 105.0% of the labeled amount.

Smith-Dorsey, Division of the Wander Company, cooperated by furnishing scientific data to aid in developing this monograph.

Carbinoxamine Maleate.—$C_{16}H_{19}ClN_2O.C_4H_4O_4$.— M.W. 406.88. — 2-[*p*-Chloro-α-(2-dimethylaminoethoxy)benzyl]pyridine maleate. — The structural formula of carbinoxamine maleate may be represented as follows:



Physical Properties: Carbinoxamine maleate is a white, odorless, bitter, crystalline powder. It melts at 116-119°. It is very soluble in water, freely soluble in alcohol and in chloroform, and very slightly soluble in ether. The pH of a 1% solution is 4.6-5.1.

Identity Tests: Dissolve about 0.1 gm. of carbinoxamine maleate in 2 ml. of water and divide the solution into two equal portions. Dip a clean copper wire in one portion and hold it in the nonluminous portion of the flame of a Bunsen burner: the flame turns green (*presence of chlorine*). To the second portion add 1 ml. of ammonium reineckate T. S.: a pink precipitate forms.

A 0.0025% solution, prepared as directed in the spectrophotometric assay for carbinoxamine maleate, exhibits an ultraviolet absorbance maximum at about 261 mμ [absorptivity (1%, 1 cm.), about 138], a slight inflection at about 255 mμ and a minimum at about 245 mμ.

Purity Tests: Dissolve about 0.3 gm. of carbinoxamine maleate in 2 ml. of alcohol, add 5 drops of chloroform and 0.5 ml. of 50% potassium hydroxide, and heat: a yellow color develops, but no odor of isonitriles (*absence of primary amines*).

Dry about 1 gm. of carbinoxamine maleate, accurately weighed, in a vacuum desiccator over phosphorus pentoxide for 3 hours: the loss in weight does not exceed 0.5%.

Char about 1 gm. of carbinoxamine maleate, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.1%.

Assay: (Carbinoxamine Maleate) Prepare a 0.0025% solution of carbinoxamine maleate as follows: Transfer to a 100 ml. volumetric flask 0.25 gm. of carbinoxamine maleate, accurately

weighed, fill to the mark with water, and mix. Transfer to a second 100 ml. flask 10 ml. of this solution, fill to the mark with water, and mix. Transfer to a third 100 ml. volumetric flask 10 ml. of this last solution, fill to the mark with water, and mix. Spectrophotometrically determine the absorbance in a 1 cm. quartz cell at 261 mμ, using water as a blank. The concentration of anhydrous carbinoxamine maleate in the solution in mg./ml. = absorbance ÷ 13.8. The amount of carbinoxamine maleate is not less than 95.0 nor more than 105.0%.

(Nitrogen) Transfer to a semimicro Kjeldahl flask about 0.15 gm. of carbinoxamine maleate, accurately weighed, and digest it for 4 hours with 7 ml. of sulfuric acid, 2.7 gm. of potassium sulfate, and 0.3 gm. of mercuric oxide. Cool the flask, add 15 ml. of water, cool it again, connect it to an ammonia-distillation apparatus, and add 30 ml. of 40% sodium hydroxide and 10 ml. of 40% sodium thiosulfate. Distil the ammonia into 20 ml. of 4% boric acid. Using a mixed indicator (1:5 methyl red T. S. and bromocresol green T. S.), titrate the solution with 0.05 *N* sulfuric acid. Each milliliter of 0.05 *N* acid is equivalent to 0.0007004 gm. of nitrogen and 0.01017 gm. of anhydrous carbinoxamine maleate. The amount of nitrogen is not less than 6.68 nor more than 7.09%, equivalent to not less than 97.0 nor more than 103.0% of carbinoxamine maleate.

Dosage Forms of Carbinoxamine Maleate

ELIXIRS. *Identity Tests:* The pink precipitate formed on the addition of ammonium reineckate T. S. in the assay for carbinoxamine maleate serves as an identity test for this substance.

Assay: (Carbinoxamine Maleate) Transfer to a 50 ml. volumetric flask a volume of elixir, accurately measured, equivalent to about 20 mg. of carbinoxamine maleate, fill to the mark with 2% v/v sulfuric acid, and mix. Transfer to one of two 50 ml. beakers 20 ml. of this sample solution. To the second beaker add 20 ml. of solution A (0.04% carbinoxamine maleate in 2% v/v sulfuric acid prepared from carbinoxamine maleate, N. N. R.). To both beakers add 5 ml. of 1% v/v sulfuric acid and 5 ml. of ammonium reineckate T. S., and mix. Allow the beakers to stand 1 hour in a refrigerator, then filter with suction each mixture through a medium-porosity sintered-glass funnel. Use portions of the filtrate to transfer each precipitate completely to the funnel, and wash each one with three 2 ml. portions of ice-cold water. Continue drawing air through the filter funnels until the precipitates are dry. Place test tubes under the stems of the funnels in the suction flasks and, with the aid of suction, wash each precipitate into a test tube with five 1 ml. portions of acetone. Transfer the filtrates to 25 ml. volumetric flasks, rinse the test tubes with acetone, fill to the mark with acetone, and mix. Spectrophotometrically determine the absorbances in 1 cm. cells at 525 mμ, using acetone as a blank. The concentration of anhydrous carbinoxamine maleate in the aliquot taken for assay in mg./ml. = 0.4 (absorbance of sample ÷ absorbance of solution A). The amount of carbinoxamine maleate is not less than 93.0 nor more than 107.0% of the labeled amount.

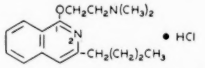
(Alcohol) To 50 ml. of elixir add 50 ml. of water and on the solution run a *U. S. P. alcohol determination*. The amount of alcohol is not less than 85.0 nor more than 115.0% of the labeled amount.

TABLETS. *Identity Tests:* The tablets respond to the spectrophotometric identity test for the active ingredient in the monograph for carbinoxamine maleate.

Assay: (Carbinoxamine Maleate) Weigh 20 tablets and powder them. Transfer to a 100 ml. volumetric flask an amount of powder, accurately weighed, equivalent to about 25 mg. of carbinoxamine maleate, add 50 ml. of water, and shake the flask mechanically for 15 min. Fill to the mark with water and mix. Centrifuge a portion of the solution. Transfer to a second 100 ml. volumetric flask 10 ml. of the clear supernatant solution, fill to the mark with water, and mix. Spectrophotometrically determine the absorbance in a 1 cm. quartz cell at 261 mμ, using water as a blank. The concentration of anhydrous carbinoxamine maleate in the solution in mg./ml. = absorbance ÷ 13.8. The amount of carbinoxamine maleate is not less than 95.0 nor more than 105.0% of the labeled amount.

McNeil Laboratories, Inc., cooperated by furnishing scientific data to aid in developing this monograph.

Dimethisoquin Hydrochloride.—$C_{17}H_{21}N_2O.HCl$.—M.W. 308.86.—3-Butyl-1-(2-dimethylaminoethoxy)-isoquinoline hydrochloride.—The structural formula of dimethisoquin hydrochloride may be represented as follows:



Physical Properties: Dimethisoquin hydrochloride is a white powder with a bitter, numbing taste and a slight aromatic odor. It melts at 144.0-147.0°. It is freely soluble in alcohol and very slightly soluble in ether. The approximate amount that dissolves at 25° in 100 ml. of water is 5 gm. The pH of a 1% solution is 3.5-5.0.

Identity Tests: Dissolve about 0.5 gm. of dimethisoquin hydrochloride in 12 ml. of water, add 1 ml. of sodium hydroxide T. S., and transfer the mixture to a 60 ml. separatory funnel. Extract the liberated base with one 10 ml. portion of ethyl acetate. Dry the extract over anhydrous sodium sulfate for 10 min. Filter the mixture through a dry filter paper and collect the filtrate in a test tube. Add 0.5 ml. of methyl iodide, warm the mixture in a boiling water bath for 3 min., and cool in an ice bath. Filter the mixture, recrystallize the precipitate from anhydrous methanol, and dry the crystals at 105° for 30 min.: the methyl iodide quaternary ammonium salt melts at 179-181°.

A 0.002% solution, prepared as directed in the spectrophotometric assay for dimethisoquin hydrochloride, exhibits ultraviolet absorbance maxima at about 273 mμ [absorptivity (1%, 1 cm.), about 241], 284 mμ [absorptivity (1%, 1 cm.), about 215], 315 mμ [absorptivity (1%, 1 cm.), about 122], and 329 mμ [absorptivity (1%, 1 cm.), about 115]; and minima at about 281 and 300 mμ. The ratio of the absorbances at 274 and 329 mμ is 2.07-2.13.

Purity Tests: Dry about 1 gm. of dimethisoquin hydrochloride accurately weighed, at 105° for 3 hours: the loss in weight does not exceed 2.0%.

Char about 1 gm. of dimethisoquin hydrochloride, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 0.05%.

Assay: (Dimethisoquin Hydrochloride) Prepare a 0.002% solution of dimethisoquin hydrochloride as follows. Transfer to a 100 ml. volumetric flask 0.1 gm. of dimethisoquin hydrochloride, accurately weighed, fill to the mark with isopropanol, and mix. Transfer to a second 100 ml. volumetric flask 10 ml. of this solution, fill to the mark with isopropanol, and mix. Transfer to a third 100 ml. volumetric flask 20 ml. of this last solution, fill to the mark with isopropanol, and mix. Spectrophotometrically determine the absorbance in a 1 cm. quartz cell at 329 mμ, using isopropanol as a blank. The concentration of anhydrous dimethisoquin hydrochloride in the solution in mg./ml. = absorbance ÷ 11.5. The amount of dimethisoquin hydrochloride is not less than 95.0 nor more than 105.0%.

(Chloride) Transfer to a 250 ml. glass-stoppered Erlenmeyer flask about 1.0 gm. of dimethisoquin hydrochloride, accurately weighed. Dissolve the powder in 50 ml. of water. Add 50 ml. of 0.1 *N* silver nitrate, accurately measured, 5 ml. of nitric acid, and 3 ml. of nitrobenzene. Mix and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate, using 2 ml. of ferric ammonium sulfate T. S. as an indicator. Each milliliter of 0.1 *N* silver nitrate consumed is equivalent to 0.003546 gm. of chloride and 0.03088 gm. of anhydrous dimethisoquin hydrochloride. The amount of chloride is not less than 11.3 nor more than 11.7%, equivalent to not less than 98.0 nor more than 102.0% of dimethisoquin hydrochloride.

Dosage Forms of Dimethisoquin Hydrochloride

LOTIONS. *Identity Tests:* A 0.002% solution, prepared as directed in the spectrophotometric assay for dimethisoquin hydrochloride, exhibits ultraviolet absorbance maxima at about 315 and 329 mμ.

Assay: (Dimethisoquin Hydrochloride) Transfer to a 50 ml. volumetric flask an amount of lotion, accurately weighed, equivalent to about 10 mg. of dimethisoquin hydrochloride, fill to the mark with isopropanol, and mix. Centrifuge a portion of the solution. Transfer to a second 50 ml. volumetric flask 5 ml. of the clear supernatant liquid, fill to the mark with isopropanol, and mix. Spectrophotometrically determine the absorbance in a 1 cm. quartz cell at 329 mμ, using isopropanol as a blank. The concentration of anhydrous dimethisoquin hydrochloride in the solution in mg./ml.=absorbance÷11.5. The amount of dimethisoquin hydrochloride is not less than 90.0% of the labeled amount.

OINTMENTS. *Identity Tests:* The ointment responds to the spectrophotometric identity test for the active ingredient in the monograph for dimethisoquin hydrochloride.

Assay: (Dimethisoquin Hydrochloride) Transfer to a 50 ml. volumetric flask an amount of ointment, accurately weighed, equivalent to about 10 mg. of dimethisoquin hydrochloride, fill to the mark with isopropanol, and mix. Centrifuge a portion of the solution, if necessary. Transfer to a second 50 ml. volumetric flask 5 ml. of clear supernatant solution, fill to mark with isopropanol, and mix. Spectrophotometrically determine absorbance in a 1 cm. quartz cell at 329 mμ, using isopropanol as a blank. The concentration of anhydrous dimethisoquin hydrochloride in the solution in mg./ml.=absorbance÷11.5. The amount of dimethisoquin hydrochloride is not less than 95.0 nor more than 105.0% of the labeled amount.

Smith, Kline & French Laboratories cooperated by furnishing scientific data to aid in developing this monograph.

Erythromycin Ethyl Carbonate.—Erythromycin ethyl carbonate is the ethyl carbonate ester of erythromycin, an antibiotic produced by the growth of Streptomyces erythreus Waksman. The chemical structure of erythromycin ethyl carbonate has not been established.

Physical Properties: Erythromycin ethyl carbonate is a white, practically odorless powder having a very slightly bitter taste. It is freely soluble in alcohol and practically insoluble in water. The amount that dissolves in ether to form 100 ml. of solution is about 5 gm.

Identity Tests: Transfer to a test tube about 10 mg. of erythromycin ethyl carbonate and add about 2 ml. of hydrochloric acid: a yellow color appears and changes to dark greenish yellow.

Transfer to a test tube about 5 mg. of erythromycin ethyl carbonate, and add 5 ml. of sulfuric acid and shake gently: a red-brown color appears.

A 2% solution of erythromycin ethyl carbonate in alcohol is levorotatory.

Purity Tests: On about 0.5 gm. of erythromycin ethyl carbonate, accurately weighed, run a *U. S. P. Karl Fischer test for water:* the amount of moisture does not exceed 5.0%.

Char about 0.5 gm. of erythromycin ethyl carbonate, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 1.0%.

Assay: (Erythromycin) Transfer to a 100 ml. volumetric flask 27.4 mg. of erythromycin ethyl carbonate, accurately weighed, and add 40 ml. of methanol. Fill to the mark with water and mix. Allow the solution to stand for 48 hours. Transfer to a 500 ml. volumetric flask 2 ml. of the solution and fill to the mark with 0.1 M phosphate buffer, pH 8.0, to obtain a solution containing in each milliliter the equivalent of about 1 mcg. of erythromycin. Proceed as directed in the *U. S. P. erythromycin microbial assay.* The amount of erythromycin activity is not less than 85.0%.

Dosage Forms of Erythromycin Ethyl Carbonate

POWDER. *Identity Tests:* Erythromycin ethyl carbonate is supplied as a mixture of solids to which water is added before use to prepare a suspension. With 50 ml. of chloroform extract an amount of powder equivalent to about 0.1 gm. of erythromycin ethyl carbonate. Filter the chloroform through a dry filter paper and evaporate the filtrate to dryness in a current of warm air. The residue responds to the identity tests for the active ingredient in the monograph for erythromycin ethyl carbonate.

Assay: (Erythromycin) Transfer the entire contents of the container to a 100 ml. volumetric flask and add sufficient distilled water to make 100 ml. Mix thoroughly and transfer an aliquot portion, equivalent to 25 mg. of erythromycin, to a second 100 ml. volumetric flask, fill to the mark with water and mix. Transfer 2 ml. of the solution to a 500 ml. volumetric flask, fill to the mark with 0.1 M phosphate buffer, pH 8.0, to obtain a solution containing in each milliliter the equivalent of about 1 mcg. of erythromycin. Proceed as directed in the *U. S. P. erythromycin microbial assay.* The amount of erythromycin activity is not less than 85.0% of the labeled amount.

Eli Lilly & Company cooperated by furnishing scientific data to aid in developing this monograph.

Erythromycin Lactobionate.—Erythromycin lactobionate is the lactobionate salt of erythromycin, an antibiotic substance produced by the growth of Streptomyces erythreus Waksman. The chemical structure of erythromycin lactobionate has not been established.

Physical Properties: Erythromycin lactobionate is a white, practically odorless powder. It is freely soluble in water and alcohol, and slightly soluble in ether. The pH of a 2% solution is 6.0-7.5.

Identity Tests: Transfer to a test tube about 10 mg. of erythromycin lactobionate and add about 2 ml. of hydrochloric acid: a yellow color appears and changes to a dark greenish yellow.

Transfer to test tube about 5 mg. of erythromycin lactobionate and add 5 ml. of sulfuric acid: a red-brown color appears.

Transfer to a test tube about 50 mg. of erythromycin lactobionate and dissolve it in about 5 ml. of water. Add about 5 ml. of a saturated solution of picric acid, allow to stand for about 10 min., and filter. Wash the precipitate with water and dry in a vacuum desiccator: the picrate formed melts at 168-175° (*Caution! Picrates may be explosive*).

A 2% solution of erythromycin lactobionate in water is levorotatory.

Purity Tests: On about 0.5 gm. of erythromycin lactobionate, accurately weighed, run a *U. S. P. Karl Fischer test for water:* the amount of moisture does not exceed 5.0%.

Char about 0.5 gm. of erythromycin lactobionate, accurately weighed, cool the residue, add 1 ml. of sulfuric acid, heat cautiously until evolution of sulfur trioxide ceases, ignite, cool, and weigh: the residue does not exceed 2.0%.

Assay: (Erythromycin) Transfer to a 100 ml. volumetric flask 37.1 mg. of erythromycin lactobionate, accurately weighed, fill to the mark with water, and mix. Transfer 2 ml. of the solution to a 500 ml. volumetric flask and fill to the mark with 0.1 M phosphate buffer, pH 8.0, to obtain the assay preparation containing in each milliliter the equivalent of 1 mcg. of erythromycin as the lactobionate. Proceed as directed in the *U. S. P. erythromycin microbial assay.* The amount of anhydrous erythromycin lactobionate is not less than 85.0%.

Dosage Forms of Erythromycin Lactobionate

POWDER. *Identity Tests:* The powder responds to the identity tests for the active ingredient in the monograph for erythromycin lactobionate.

Assay: (Erythromycin) Transfer to a 100 ml. volumetric flask an amount of powder, accurately weighed, equivalent to 25 mg. of erythromycin, fill to the mark with water, and mix. Transfer to a 500 ml. volumetric flask 2 ml. of the solution and fill to the mark with 0.1 M phosphate buffer, pH 8.0, to obtain the assay solution containing in each milliliter the equivalent of about 1 mcg. of erythromycin as the lactobionate. Proceed as directed in the *U. S. P. erythromycin microbial assay.* The amount of erythromycin lactobionate is not less than 85.0% of the labeled amount.

Abbott Laboratories cooperated by furnishing scientific data to aid in developing this monograph.

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ACNE VULGARIS

GUEST EDITORIAL

Stephen Rothman, M.D.

There are many pathological conditions that never endanger but often ruin life. Foremost among these "harmless" conditions is acne of the adolescent, which in its more serious forms extends well into the third decade of life and in its scarring variety may leave unsightly pockmarks visible through a lifetime. In our age, which glorifies the unblemished milky complexion in women, and the smooth, clean-shaven face in men, the psychological, economic, and social implications of acne, as indicated in the report to the Committee on Cosmetics in this issue of THE JOURNAL (page 1117), are great.

Progress has been made during the last decade in a better understanding of the local pathogenesis and hormonal constellation of seborrhea and acne. Nutritional and climatic influences have become better appreciated, and the role of bacterial infection has been analyzed; but real progress in therapy is still missing, possibly with the remarkable exception of the perfected methods of treating pitted scars by mechanical means. While the role of "androgenic" hormonal effects on sebaceous glands and cornification of the follicular openings is fairly well understood in both men and women, the main hurdle in the therapeutic use of this knowledge is that the dosage of estrogens required to counteract the acnegenic effects is so high as not to be safe. Whether small and safe doses of estrogens, administered systemically or locally, are effective at all is still a controversial question. Therapy with vitamin A has a good rational foundation because of its well-established antikeratinizing action, but, again, its true therapeutic effectiveness is doubted by many. Modern antibiotics are often valuable in combating the pustular elements of acne, but they do not solve the basic problem.

Thus the main body of our therapeutic armamentarium is still local treatment on an empirical basis as it has been practiced for almost 100 years, and, among topically applied chemicals, sulfur is still the most effective agent. Sulfur in coarse particles in any vehicle is rather irritating to the skin. The precipitated sulfur of the United States Pharmacopeia, however, has an optimal particle size that can be incorporated uniformly into any kind of vehicle and is effective without being unduly irritating. Further decrease of the particle size to submicroscopic (colloidal) dimensions has been claimed to be even more advantageous; organic sulfur compounds have not shown any superior action. Sulfur enters the skin easily and is reduced there to sulfide and hydrosulfide ions. In this form it exerts its keratolytic and sebum-reducing effects. Salicylic acid and resorcinol often added to sulfur preparations for local application act mainly as keratolytics and pacemakers for sulfur. Ultraviolet rays have a similar action, in addition to increasing arterial blood flow.

Commercial preparations containing sulfur, salicylic acid, and resorcinol are widely available; however, as is often the case with empirical therapy, the physician prefers to choose and to change concentrations and vehicles individually, according to the type and severity of the case. Here the dermatologist practices the art rather than the science of his profession. He can do this quite successfully if he has had broad experience, provided this experience is based on close, sound, and unbiased observation; but even the most experienced, talented, and ingenious therapists will have patients who do not respond satisfactorily to empirical treatment methods.

Further basic and clinical research is badly needed in this field. Obviously, it will take time until we shall have a "routine" therapy that will not fail in any case. Until then the practitioner should learn not to minimize the significance of acne and should not try to console the patient with such platitudes as "this is nothing, every youngster must go through it" or with untrue statements such as "you will be all right as soon as you get married." He rather should encourage the patient to have treatment by a specialist. In the great majority of cases this will yield satisfactory results.

THE HOUSSAY PHENOMENON IN MAN

Simmonds [1] in 1914 described a patient with clinical symptoms suggestive of hypopituitarism and postmortem lesions the essential feature of which was the destruction of the pituitary. The syndrome represented a condition of insufficiency of the anterior lobe of the pituitary. He believed that the cause of the syndrome was the embolic closure of the arterial blood supply to the gland.

Sheehan [2] in 1938 described massive focal atrophy of the anterior lobe of the pituitary, which occurs only in women and is nearly always of postpartum origin. Hemorrhage and collapse at delivery occurred in all of his cases. Again in 1949 [3] he reported on autopsies in 95 cases culled from the literature and considered by him as examples of severe chronic hypopituitarism. The characteristic features of the chronic type of hypopituitarism are a history of severe circulatory collapse as a result of hemorrhage and shock at a delivery, atrophy of the gonads and genital tract with amenorrhea,

1. Simmonds, M.: Über Hypophysisschwund mit tödlichem Ausgang, Deutsche med. Wchnschr. **40**: 322, 1914.
2. Sheehan, H. L.: Post-Partum Necrosis of the Anterior Pituitary, Edinburgh M. J. **45**: 13 (March) 1938.
3. Sheehan, H. L., and Summers, V. K.: The Syndrome of Hypopituitarism, Quart. J. Med. **18**: 319 (Oct.) 1949.

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impotence and loss of libido, loss of pubic and axillary hair, increased sensitivity to cold, weakness, mental torpidity, insulin sensitivity, and a tendency to spontaneous hypoglycemia and coma. The number of cases of hypopituitarism from various lesions involving the pituitary has considerably increased in the last decade.

In 1930 Houssay and Biasotti [4] demonstrated in experiments the mutual antagonism between the effects of insulin and an anterior pituitary hormone upon the concentration of blood glucose. Houssay showed that diabetes induced in an animal by a pancreatectomy can be alleviated by a hypophysectomy. The same antagonism exists in man. The occurrence, however, of the so-called Houssay phenomenon in man has been rare. A recent review by Harvey and de Klerk [5] lists only 11 cases, to which they add 3 of their own. Of these 11, nine have died and have come to autopsy. In eight massive infarction of the pituitary was found. Balo, Calder, Lyall and Innes, Kotte and Vonderahe, Marzullo and Handelsman, Rothfeld and Jonas, and Williams and Brenner each have contributed to the literature a single case of Houssay phenomenon in man.

Harvey and de Klerk point out that the common complaint in all of these patients was severe headache. The complaint was made at the time infarction must have occurred in the pituitary. This was followed by attacks of hypoglycemia. Hypoglycemia continued despite the reduction in insulin dosage. The symptoms of hypoglycemia were severe and refractory to treatment with intravenously given glucose.

Pituitary insufficiency should be suspected in the diabetic whose requirement for insulin decreases very rapidly or if insulin shock occurs with frequency and hypoglycemia is resistant to the intravenous administration of glucose. The importance of recognition of the Houssay phenomenon, as pointed out by Harvey and de Klerk, is quite evident, for if insulin administration is continued in the diabetic who develops panhypopituitarism, fatal hypoglycemia may result. If the condition is recognized, treatment with adrenal cortical, thyroid, and estrogenic hormones will overcome many of the secondary effects of the disorder.

FIFTH NATIONAL CONFERENCE ON PHYSICIANS AND SCHOOLS

The fifth National Conference on Physicians and Schools was held a few weeks ago at Moraine-on-the-Lake Hotel, Highland Park, Ill. Some 200 representative of state departments of health and education, state medical associations, and national voluntary health agencies participated. Held every other year, the conference is designed to stimulate agreement on joint action by medicine, public health, and education to bring about effective health services for school children. The meetings are sponsored by the American Medical Association and conducted through its Bureau of Health Education.

Leading speakers at general sessions were Surgeon General Leonard Scheele, Public Health Service, and Commissioner Samuel Brownell, Office of Education, both of the Department of Health, Education, and Welfare; Dr. Elmer Hess, Erie, Pa., A. M. A. President; Dr. George Lull, A. M. A. Secretary and General Manager; and Mrs. Rollin Brown, Los Angeles, president of the National Congress of Parents and Teachers. Speakers agreed on a number of important points, the following ones might be singled out for special mention: The first responsibility for the health of children rests with parents; the school and other community agencies supplement and reinforce the efforts of the home. Accidents and mental health are today's major child health problems; these must be met with the same scientific approaches that have brought other important health advances. Except for general policies, no single pattern for the various aspects of the school health program can be suggested; each community needs to make adaptations in terms of local conditions, facilities, and personnel.

During the conference a number of discussion groups working with expert consultants considered a number of special problems. It is difficult to generalize their conclusions except in terms of the summaries presented at the end of the conference by three representative reporters: one for medicine, John Reichert, M.D., practicing physician, Chicago; one for education, John Miller, Ed.D., superintendent of schools, Great Neck, N. Y.; and one for public health, John Shackelford, M.D., director of local health services, Oklahoma State Health Department. This panel pointed up the need for a "team approach" in the development of the school health program. The function of the professional groups concerned, they said, is to work together effectively to assist parents to carry out their child health obligations. One of the chief accomplishments of the conference, the panel felt, was better delineation of professional responsibilities of medicine, education, and public health in the school health program. Perhaps the most important outcome, they said, was "an increased respect among the various disciplines for the professional competence and integrity of the others."

Elsewhere in this issue (see page 1126) a preliminary report on the conference is given; more comprehensive proceedings will be published later. But even the brief discussion above is sufficient to demonstrate the importance of medical participation in the formulation and development of school health programs. The House of Delegates undoubtedly had this in mind when in 1952 at the Denver meeting of the American Medical Association they commended similar conferences and other leadership efforts in school health to local and state medical societies and associations. After the fifth National Conference on Physicians and Schools the time is especially opportune. General policies for school health consistent with sound principles and practices in medicine, education, and public health have been agreed upon. In the final analysis, however, these must have their specific and practical implementation in our local schools and communities.

4. Houssay, B. A., and Biasotti, A.: La diabetes pancréatica de los perros hipofisoprivos, Rev. Soc. argent. de biol. **6**: 251, 1930.

5. Harvey, J. C., and de Klerk, J.: The Houssay Phenomenon in Man, Am. J. Med. **19**: 327 (Sept.) 1955.

ORGANIZATION SECTION

SCHOOL CONFERENCE ON HEALTH PROBLEMS

The emergence of the medical, education, and public health professions as a functioning "team" was a major theme of the fifth National Conference on Physicians and Schools, held at Highland Park, Ill., Oct. 12-14. More than 200 physicians, public health officials, educators, and representatives of related organizations participated in round-table discussions at the conference, sponsored biannually by the American Medical Association and its Bureau of Health Education. Thirty-four states and the District of Columbia were represented by the conferees.

Viewpoints of education, public health, medicine, and the home were shown at the opening session by Samuel Brownell, Ph.D., commissioner, Office of Education, and Dr. Leonard Scheele, surgeon general, Public Health Service, both of the Department of Health, Education, and Welfare; Dr. George F. Lull, Secretary and General Manager of the A. M. A., and Mrs. Rollin Brown, president, National Congress of Parents and Teachers. These speakers agreed that more home and community participation and more emphasis on mental health and accident prevention is needed.

Dr. Scheele said at present rates it is estimated that "one out of every 12 children will spend some time in mental institutions. Among children 5-14 years old 40 per cent of all deaths are due to accidents." He said the Department of Health, Education and Welfare wishes to know what specific help the federal agencies can give states and communities. Such programs, he noted, would have to be geared to fit individual localities and situations. Dr. Lull said that "by every solid measure of health" our youth is healthier than ever before: longer years of life are in store; their chances of living to school age are better than at any previous time; their chances of living through the school years have reached an all-time high; youngsters are bigger and heavier on the average than ever; and gains against disease have been "phenomenal." Except for accidents, which are responsible for more deaths and disabilities among children than the next several causes combined, he said, we have made "excellent progress" on all fronts. He outlined a five-point program for improving school health, including: an accident prevention program and procedures to meet emergencies at school; preventive work in mental health; discovery and follow-up of children with health problems; full use of the school's special opportunities for health education; and interpretation of health needs and services to parents and other adults.

Dr. Brownell listed a number of major improvements resulting from cooperation among educators and health specialists, including gains in extent and coverage of health services; better health education programs in preparing teachers; improvement of health text books, films, teacher's guides, and other educational material; major changes in standards of lighting, heating, ventilation, acoustics, sanitation and provision of health, athletic, and washing facilities; great increases in enrollment of children in health and physical education classes; increased health awareness and education of parents and public; and expanded knowledge of how children grow and learn. In any community, medical and dental services, water supply and waste disposal, restaurant sanitation, adult health education, advertising mediums and hundreds of other forces all "make their impact on the school child's health—and that of his family and teachers," Dr. Brownell said. "These forces also influence directly or indirectly most of his educational experiences." He said interrelationships between professional persons and others involved in the school child's health must be "real and vital" if all children are to be best served.

Mrs. Brown described the mushrooming interest of the Parents and Teachers Congress in various aspects of the child's welfare and noted that the entire community is involved in this question. "Health really is everybody's business," she said. "Programs of any kind will fail unless they have public approval. Like radio and TV, you can always turn off a program if it bores you or propagandizes. But everyone has a real interest in something to which he can devote his own thought, time and energy—even more than his money."

TWO MAJOR JOBS

Dr. Elmer Hess, Erie, Pa., President of the A. M. A., told participants that two of their biggest jobs should be in cutting down street and highway accidents and helping the child with emotional or mental problems. He said teachers must first discover and then help the child with such difficulties, because some children just "can't take" usual educational methods. "All children are not created mentally and physically equal," he said, "We must find the one who has problems, spot him early, and guide him if possible" so he is "kept from growing up a disgrace, a menace, or worse still, the forgotten soul in a mental institution." Three ways Dr. Hess suggested to combat highway accidents were: to encourage auto manufacturers to install safety devices to such an extent that in an accident, injuries would be reduced to a minimum; insist on law enforcement, including restriction on too-slow drivers as well as speeding ones; and "most important," urge that no one be allowed to drive who is not in perfect mental and physical health.

REPORT OF CONCLUSIONS

At the formal session closing the conference, a new approach to a general report on its activities was used. "Roving reporters" who had visited the various discussion groups gave highlights from each group and then a general "summing up." The reporters, representing the three major fields involved—medicine, public health, and education—were Dr. John Miller, Ed.D., superintendent of schools, Great Neck, N. Y.; Dr. John Shackleford, Oklahoma state Department of Health; and Dr. John

Reichert, American Academy of Pediatrics. They noted that one of the major feelings of the conference was "an increased respect among the various disciplines for the professional competence and integrity of the others." Discussing the central theme, a "team approach," they said the function of the interrelated professional groups, working cooperatively, is to help parents in discharging their responsibility in the proper care of their children. The feeling was that the relations between members of the team should be such that any member would feel free to initiate action or propose changes. A big step forward in the conference, they said, was the spelling out in more detail of areas of responsibility of the members of the team. They also said the various groups, in their discussions, seemed to be getting into an important concept—that of the "total child."

The child, it appeared to conferees, is not just a physical entity "who shows up in school each day" but a human being with physical, emotional, social, and moral aspects that those who deal with children must recognize and guide. The child also is not just a school child but member of family and a community with problems in each area. The team therefore is ideally representative of the entire community of the child's environment.

Some of the highlights of the 10 discussion groups and some conclusions drawn by each group follow. The group discussing "Use of Health Records," under the chairmanship of Dr. A. B. Rosenfield, Minnesota Department of Health, Minneapolis, said there should be cumulative health records on each school child, including teacher observations, history of illness and immunization, and recommendations from the physician. The record could be used as a tool for nurse-teacher conferences and referrals. This group also urged "an intelligent interchange of information with the consent of the family, on a professional and confidential basis."

The teacher—who represents the known and familiar—should play the central role in preparation for and handling of disasters at school, according to a group which had as its chairman August Pritzlaff, Chicago Board of Education. Since panic results largely from the unknown, any plan for disaster should require that the teacher remain in control of her pupils. Preparations involve routine procedures, psychological adjustment, and cooperation with civil defense, fire authorities, the medical profession and others.

Comics, Movies, and Television.—An interesting highlight of the discussion group periods was the appearance of four teen-agers from a nearby school, in the section considering the health aspects of comics, movies, and television, directed by Elizabeth Avery, Ph.D., Washington, American Association of Health, Physical Education and Recreation. The four students, who were exceptionally poised and enthusiastic in answering the discussants' questions, seemed to feel that perhaps "the grown-ups" were worrying too much about the problem. They agreed that if teen-agers have enough interesting and important activities (such as sports, musical groups, student and civic activities) the mass entertainment mediums will hold only an appropriate place. They admitted that the elementary school level problem is different and that some of the younger boys and girls spend an inordinate amount of time at television or comic books.

The group generally agreed—assuming that accuurate studies on the problem are done—that guides for parents could be developed to use in handling their own family situations. They said the problem is largely one of "too much time spent in sedentary entertainment," regardless of the merits of the television programs or comic books. However, they suggested that programs for young people might take advantage of opportunities to present information on health and safety. Joint action by parent groups with the assistance and guidance of the school, public health, and medicine is needed to analyze good and bad entertainment and to budget the child's time within a variety of wholesome activities, the group said.

Athletic Activities.—Athletic activities and their emotional aspects were discussed by the group with Dr. George Maksim, District of Columbia Medical Association, as chairman. They suggested that a different approach is needed for children up to 12 and those over 12. In the young group, athletic activities should: (1) be adapted to growth patterns of the individual, (2) encourage maximum participation by breaking big groups up into small ones, (3) involve both cooperation and competition adapted to the age and maturity of the pupils, (4) afford opportunity for the child to succeed, (5) reduce unfavorable emotional responses to a minimum, and (6) recognize motivations of the pupils. For the older groups, activities should: (1) help students develop a sense of values, independence, and cooperation, (2) recognize characteristics of adolescence, (3) be comprehensive, including individual, group and coeducational activities, (4) reduce unfavorable emotional responses to a minimum, (5) be on an intramural basis in the junior high schools and for girls in the senior high schools, (6) keep exhibitionism at a minimum, (7) be supported by sound administrative practices, and (8) be an integral part of the educational program and be so financed. The group added a note that motivations of adults planning sports programs for children should be carefully studied.

Health Counseling and Personality Problems.—Another group defined its subject, health counseling, as "the continuous process of helping the pupil and parents to gain insight and understanding into the status of the pupil's mental and emotional health." With Mabel Rugen, Ph.D., of the University of Michigan, as chairman, the group said counseling for healthful living should be available to all students, and should be coordinated with other counseling programs. Urging that counseling should be available first to those who have apparent need for it but also to those who do not appear to need help, the group commented that "nonrecognition of a problem is no guarantee that none exists."

The child as a "totality" was an important consideration of the group discussing personality and behavior problems, with Dr. C. Morley Sellery, Los Angeles City Board of Education, as chairman. It said such problems have an impact on the "whole child" and on the educational program. The teacher as a "team member" must

be broadly educated, especially in child growth and development, so that he may prevent, recognize, and solve problems within his competence. Both parents and prospective parents should be educated to assume their responsibilities, while all groups concerned with emotional health should arrange for the proper professional interchange of information. Every community should have available child guidance facilities, the group said, and regional and state groups should encourage setting up of study groups on emotional health problems.

Cooperation and Activity.—Effective home-school cooperation is important because the child's needs are better met and the administrator can relate education to the parents' objectives and community needs, according to the group headed by Dr. Guy N. Magness, Missouri State Medical Association. This group said communication must be two-way: the health of the child is a family responsibility; and parents, teachers, and physicians must develop mutual understanding of their responsibilities and goals. The group noted that home visits by teacher and nurse are of great value.

"Activity is the law of childhood," one group said, and "direction of this activity in accordance with the child's developmental needs is the responsibility of all of us who are concerned with guiding him into optimum health and maturity." This group, headed by Dr. Edward A. Piszczek, of the Suburban (Cook County) Tuberculosis District, said: 1. Activity must be balanced. 2. It must be in keeping with the child's physical, emotional and social level of development. 3. It must be adapted to his interests, abilities, and temperaments, since what may be an underload for one can be an overload for another. "Firm, kind guidance, not catering to whims, is needed." 4. Underactivity can be as harmful as overactivity. 5. Activities of the handicapped must be modified by consultation with medical advisors and other specialists. 6. The gifted child needs careful and individual evaluation of his health needs. 7. The proper diagnosis of activity needs and problems can be arrived at only by close consultation among teachers, parents, and medical advisors.

School Personnel and the Physician.—The group discussing preparation of school personnel in health, directed by Clifford L. Brownell, Ph.D., of Teacher's College, Columbia, N. Y., in supporting recommendations of previous conferences suggested that all elementary teachers should have the following preparation: (1) adequate information on what to look for in the daily observance of the health status of children, (2) screening tests, in cooperation with local specialists, (3) two-way cooperation between education and medicine, and (4) health education courses developed with representatives of local physicians on curriculum committees.

More practicing physicians need to be involved in the school health program, according to a group headed by Dr. Albert C. Daniels, California Medical Association, San Francisco, which discussed the personal physician and school health. The group said essentials in cooperation were to work through the local or state medical and dental societies and for the school to adopt the accepted local medical practices. It urged development of committees providing a two-way orientation opportunity for the practicing physician, the school, the others involved.

NEED FOR DIRECTION

The closing speaker for the conference, the Rev. Rex Knowles, pastor of the Presbyterian-Congregational Fellowship at the University of Nebraska, said teachers and others should not worry so much about children going wrong as about their "not going anywhere at all." He said young people now are often "spiritually unemployed" and need direction in knowing "who they are working for and who they are." "Isn't it the responsibility of the schools to find students who are blind to their potentials, the needs of the world, and how their potentials can meet these needs," he said. "The success pattern of our schools forgets 'the small' and doesn't give it a chance to hold up its head. These youngsters can be told that each person is needed, each living a little, dying a little and doing a little. They need to know that their contributions, however small, we greatly need."

Among A. M. A. participants in the program were Dr. W. W. Bauer, Director of the Bureau of Health Education; Fred V. Hein, Ph.D., and Dr. Donald A. Dukelow, consultants in health and fitness for the Bureau; Dr. William W. Bolton, associate director of the Bureau, and Leo E. Brown, Director of Public Relations, all from Chicago.

NEW ASSISTANT TO COUNCIL SECRETARY

The Board of Trustees recently approved the appointment of Dr. Glen R. Shepherd of Kansas City, Kan., as assistant secretary of the Council on Medical Education and Hospitals. Dr. Shepherd will spearhead the Council's activities in the area of postgraduate medical education. Since 1947, Dr. Shepherd has been on the faculty of the School of Medicine of the University of Kansas and served as assistant to the dean since 1949. In announcing the appointment, Dr. Edward L. Turner, Council Secretary, said that "the increasing interest and challenge in the field of postgraduate medical education makes it important that the Council actively follow through on the findings of the recent survey in this field. Further review and study with recommendations as to the best ways and means of aiding postgraduate medical education will be part of Dr. Shepherd's assignment."

"MARCH OF MEDICINE" ON TELEVISION

Original plans for the fall series of "March of Medicine" television programs announced last summer have been changed. Instead of three, there will be two shows in this series. The next presentation, originating from the American Medical Association's Clinical Session in Boston, will be a report on alcoholism. The latest tabulation of audiences seeing A. M. A. television films "Operation Herbert" and "A Life to Save" total 7,500,000 and 9,100,000 viewers respectively.

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MEDICAL NEWS

ALABAMA

Physicians Invited to Meeting at Fort Rucker.—Physicians practicing within 100 miles or so of the Army Aviation Center, Fort Rucker, Ala., are cordially invited to a medical meeting in the fort's hospital mess hall (building no. 8766) Thursday evening, Nov. 17. The speakers will be Col. William H. Byrne, flight surgeon, whose subject will be "Medical Selection and Utilization of Helicopter Pilots," and Dr. J. F. Hammond, of Chicago, Associate Editor of THE JOURNAL, who will give an illustrated talk on "Some of the Activities of the American Medical Association." A fellowship hour at 6:30 p. m. and dinner ($1.00) at 7 p. m. will precede the program, which begins at 8 p. m.

ARIZONA

Southwestern Medical Association.—The annual meeting of this association (Dr. Joseph Bank, Phoenix, president) will be held in conjunction with the second annual Conference on Recent Advances in Medicine of the Maricopa County Medical Society (Dr. Carlos C. Craig, Phoenix, president), at the Hotel Westward Ho, Phoenix, Nov. 16-18. The program includes the following first presentations by guest speakers:

Prophylaxis and Treatment of Complications Following Biliary Tract Surgery, L. Kraeer Ferguson, Philadelphia.
The Adrenals, William E. Ehrich, Philadelphia.
Clinical Disturbances of the Pituitary Gland, Edward H. Rynearson, Rochester, Minn.
Treatment of Atrial and Septal Defects, John W. Kirklin, Rochester, Minn.
Essential Pulmonary Hypertension, Hans H. Hecht, Salt Lake City.
Hip Disorders in Children, Ignacio V. Ponseti, Iowa City.
Fungous Diseases, J. Walter Wilson, Los Angeles.
Effect of Drugs on Pulmonary Circulation and on the Control of Respiration, John L. Webb, Ph.D., Los Angeles.
Clinical Observations of the Value of Pulmonary Function Studies, Reginald H. Smart, Los Angeles.
Cataract Surgery, Kenneth L. Roper, Chicago.

There will be symposiums on regional enteritis and enterocolitis; orientation of massive bleeding from the upper alimentary tract; experience with subtotal gastrectomy in the management of peptic ulcer—postgastrectomy sequelae; prevention of malignant neoplasm of the gastrointestinal tract; and surgical evaluation of acquired heart disease.

CALIFORNIA

The Herzstein Lectures.—Dr. Howard A. Rusk, chairman of physical medicine and rehabilitation, New York University-Bellevue Medical Center, New York, will have as his general subject for the Herzstein Lectures "Medicine's Number One Problem." The University of California School of Medicine, San Francisco, will sponsor the series in the May T. Morrison Auditorium, California Academy of Sciences, Golden Gate Park, Nov. 14-16. Dr. Rusk will discuss on Monday "The Dynamics and Organization of a Modern Rehabilitation"; on Tuesday, "Clinical Problems in Rehabilitation"; and on Wednesday, "The Challenge of Gerontology."

Benefit Concert by Doctors' Symphony.—The second annual concert of the Los Angeles Doctors' Symphony Orchestra will be presented for the benefit of the Los Angeles County Physicians Aid Association Nov. 19, 8:30 p. m., in the Philharmonic Auditorium. The orchestra, composed of nearly 100 members, is under the direction of William Van den Burg, former assistant conductor of the Philadelphia Orchestra. Concert master is Dr. Benjamin Gross, Beverly Hills, who formerly held a similar position in the Louisville Symphony Orchestra. Assistant concert master is Dr. Reuben Straus, Burbank, who is also president of the symphony organization. Dr. Jerome M. Kummer, Santa Monica, is vice-president, and Dr. Elizabeth Mason Hohl, Los Angeles, president of the Physicians Aid Association, serves as impressario for the orchestra. Information may be obtained from Mrs. Virginia L. Brown, Executive Secretary of the Physicians Aid Association, 1234 N. Vermont Ave., Los Angeles 29, NOrmandy 3-1062.

Los Angeles Midwinter Medical Convention.—"Eighty-Five Years of Medical Progress" will be the theme of the Los Angeles Midwinter Medical Convention, which will be held Jan. 3-5, 1956, at the Biltmore Hotel and the Philharmonic Auditorium under the auspices of the Los Angeles County Medical Association (Dr. Ewing L. Turner, president). A half day will be devoted to each of the following subjects: "Medicine's Role in the Atomic Age," "Modern Concepts in the Utilization of Blood and Blood Products," "Diagnosis and Treatment of Neoplastic Diseases," "Preventive Medicine," "The Use and Misuse of Miracle Drugs," and "Management of the Geriatric Patient." Panel discussion moderators include: Karl Meyer, Ph.D., San Francisco; Dr. George T. Pack, New York; Dr. Oscar B. Hunter, Washington, D. C.; Dr. Edmund V. Cowdry, St. Louis; Dr. Perrin H. Long, Brooklyn, N. Y.; and Dr. Stafford L. Warren, Los Angeles. Dr. Elmer Hess, Erie, Pa., President of the American Medical Association, will speak at the anniversary dinner Tuesday in the Biltmore Bowl. Among the participants in the anniversary convention will be Dr. Dwight H. Murray, Napa, A. M. A. President-Elect. A 10 day cavalcade of health and medical progress (Jan. 6-15) will be staged at the Shrine Auditorium and Convertion Hall. The annual Tournament of Roses festivities in Pasadena, including the Rose Parade and the Rose Bowl football game on New Year's Day, precede the midwinter convention.

CONNECTICUT

Society News.—The Yale Medical Society will present the following program at 8:15 p. m., Nov. 14, in the Fitkin Amphitheatre, Yale-New Haven Medical Center:

Chelation in Contrast Radiography, Robert Shapiro, New Haven.
Epidemiology of Enteric Virus Infections, Joseph L. Melnick, Philadelphia.
Fate of Plasma Lipids in Vascular and Avascular Connective Tissue, Levin L. Waters, New Haven.
Pathogenesis of Fever, Elisha Atkins, St. Louis.

DISTRICT OF COLUMBIA

University News.—The Gamma chapter of Alpha Omega Alpha was recently installed at the Howard University College of Medicine, Washington, D. C. The charter was presented by Dr. Walter L. Bierring, Des Moines, Iowa, national president of Alpha Omega Alpha and a Past-President of the American Medical Association. The initiates were charged and presented keys by Dr. Josiah J. Moore, Chicago, national secretary-treasurer of Alpha Omega Alpha and A. M. A. Treasurer. The address of the evening was delivered by Aura E. Severinghaus, Ph.D., associate dean of Columbia University College of Physicians and Surgeons, New York, on "Reflections on Our Education."

FLORIDA

Professor of Pathology Appointed.—The University of Florida College of Medicine, Gainesville, announces the appointment of Dr. Joshua L. Edwards as professor and head of the department of pathology. Dr. Edwards has been assistant in the department of pathology and microbiology, Rockefeller Institute for Medical Research, since September, 1953.

Alcoholic Rehabilitation Program.—The Florida Alcoholic Rehabilitation Program offers 10 scholarships for the 1956 Yale Summer School of Alcohol Studies, conducted at Yale University, New Haven, Conn., during a four-week period. Scholarships will be open until Feb. 15. Inquiries should be addressed to the Florida Alcoholic Rehabilitation Program in Avon Park.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

First Unit of Medical School Dedicated.—The first building of the University of Miami School of Medicine, the outpatient clinic at Jackson Memorial Hospital, Miami, was dedicated July 17. Jay F. W. Pearson, Ph.D., president of the university, had as his topic, "Miami Comes of Age in Medicine." Dr. Pearson said in part: "I pay tribute here to those unsung heroes who accomplished legislation, fought endless legal battles, and had the vision and faith and courage to make dreams into reality. But my major tribute must be paid to those members of the medical profession, without whose devotion and selflessness you could not operate this hospital and clinic, and without whom the university could not operate a School of Medicine." He pointed out that professional treatment of the county's indigent patients would raise taxes several million dollars a year, without the volunteer service of local physicians rendering free service at the clinic and countless hours of free teaching service to students during their final two years of hospital and clinical education. Dr. Charles C. Hillman, executive director of Jackson Memorial Hospital since December, 1949, has been named associate dean of the school of medicine, and Dr. Kermit H. Gates, formerly deputy commander of Walter Reed Army Hospital at Washington, D. C., is the executive director. Dr. Hillman is a retired brigadier general whose last army post was as commanding general at Letterman General Hospital in San Francisco from 1944 to 1946.

GEORGIA

University News.—Dr. Benjamin R. Gendel, formerly chief of medicine at the Veterans Administration Hospital (Kennedy), Memphis, Tenn., has been appointed clinical professor of medicine at Emory University School of Medicine, Atlanta, and chief of medicine, Atlanta Veterans Administration Hospital.——Emory University announces the following faculty additions on a voluntary (part-time) basis in the medical school: Dr. John T. Godwin, Dr. Hugh V. Bell, Dr. Robert P. Coggins, Dr. A. Hamblin Letton, Dr. Lamar B. Peacock, Dr. Charles E. Todd; and in basic sciences in the health services, William B. Redmond, Ph.D.

ILLINOIS

Narcotic Violation.—Dr. Edward F. Cox, Neustadt Building, LaSalle, pleaded guilty in the U. S. District Court at Peoria, July 11, to a charge of violating the federal narcotic law. On Sept. 20 Dr. Cox received a suspended sentence and was placed on probation for two years. He was also fined $3,000.

Home Study Course.—Advanced training for laboratory workers is available through a correspondence course at the University of Chicago. "Principles of Pharmacology (Pharmacology 202)" is offered especially for laboratory workers who need a sound knowledge of pharmacology but have no formal training in the field; for research workers having bachelor's or advanced degrees in chemistry, biochemistry, biology, or allied fields; and for persons whose locations or work schedules prevent them from attending classes. The syllabus for the course was prepared by Valeska Evertsbusch, Ph.D., instructor for the course, in consultation with other departmental faculty members, under the supervision of Dr. Eugene M. K. Geiling, chairman of the department. "Principles of Pharmacology" covers (with exception of the laboratory work) essentially the same ground as does pharmacology in the medical curriculum of the university. As a correspondence course, it covers the field at a theoretical level. Registrations are accepted at any time. Tuition ($39) includes a 100 page syllabus and individual instructional service. Textbooks are extra. The course carries three and one-third semester hours of credit, on completion of the 30 lessons and final examination.

Chicago

Public Meeting on Diabetes.—The service unit of the Chicago Diabetes Association will conduct a free public meeting Nov. 18, 8 p. m., in the John B. Murphy Memorial Auditorium of the American College of Surgeons, 50 E. Erie St. Dr. Frederick W. Williams, New York, a vice-president, American Diabetes Association, will discuss "Living with Diabetes."

Dickinson Memorial Lecture.—At an open meeting the Chicago Academy of Sciences will present the fourth Albert Dickinson Memorial Lecture, "Some Nutritional Interrelationships of Potassium, Sodium and Nitrogen" by Dr. Paul R. Cannon, chairman, department of pathology, University of Chicago School of Medicine, at Albert Dickinson Hall (Lincoln Park—2001 N. Clark St.) Nov. 18, 8 p. m.

Fellowship in Pediatric Neurology.—A fellowship in pediatric neurology is available at the Children's Neurology Clinic of the Cook County Hospital in Chicago. It will provide clinical training in diagnosis and rehabilitation in children with neuromuscular handicaps. The trainee will be expected to participate also in a clinical laboratory problem. The annual stipend will vary from $3,000 to $5,000, depending on the qualifications of the applicant. For information write Dr. Meyer A. Perlstein, 4743 N. Drake Ave., Chicago 25.

Meeting of Cardiologists.—The Chicago Heart Association has scheduled an open meeting Nov. 15, 8 p. m., at the Drake Hotel. "Rehabilitation in Cardiovascular Disease" by Drs. Philip R. Lee and Howard A. Rusk, New York, will be presented by Dr. Lee and discussed by Dr. Ben L. Boynton. "Cerebral Atherosclerosis and the Concept of Cerebral Vasospasm" by Clark H. Millikan, Rochester, Minn., will be discussed by Dr. Geza de-Takats. All physicians are welcome. Incoming calls will be received at SUperior 7-2200.

The Jaffe Lecture.—Dr. Esmond R. Long, director of the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, will give the Richard H. Jaffe Lecture of the Institute of Medicine of Chicago at a joint meeting of the Institute of Medicine, the Chicago Pathological Society, and the Society of Medical History of Chicago in the Drake Hotel Nov. 14, 8 p. m. The meeting, which will be devoted to a memorial to the late Dr. Ludwig Hektoen, will be preceded by a dinner. This will be an open meeting. All physicians are invited.

Diabetes Detection Drive.—The Chicago Diabetes Association, with cooperation from medical and civic groups, is sponsoring a Diabetes Detection Drive as part of the annual Diabetes Week observance, Nov. 13-19. Major hospitals in the area will establish free testing centers in support of the campaign. Dr. R. Lincoln Kesler, clinical assistant professor of medicine, University of Illinois College of Medicine, and Dr. Carl A. Hedberg, chief, department of medicine, Augustana Hospital, are co-chairmen of the committee on detection and education, which includes: Dr. Henry T. Ricketts, president, American Diabetes Association; Dr. Arthur R. Colwell, president, Chicago Society of Internal Medicine; and Dr. Ford K. Hick, professor of medicine, University of Illinois College of Medicine.

KENTUCKY

Narcotic Violation.—Dr. James H. Whitson, Slaughters, was convicted in the U. S. District Court, Owensboro, Sept. 12, for violation of the federal narcotic law. On Sept. 13, Dr. Whitson was sentenced to a term of two years and was fined $6,000. The sentence was suspended, and he was placed on probation for three years.

Law Science Foundation.—The Louisville Law Science Foundation, said to be the first of its kind in the nation, was recently established as a nonprofit research and educational organization. It includes members of the Jefferson County Medical Society, Bar Association, and the University of Louisville schools of law and medicine. The board of directors consists of six physicians, six attorneys, and the deans of the law school and the medical school. Dr. R. Arnold Griswold was elected chairman; Robert W. Sloss, attorney, vice-chairman; Dr. David M. Cox, treasurer; and Theodore Wurmser, attorney, executive secretary. All are from Louisville.

Personal.—Dr. Matthew W. Meadows, Fullerton, was honored by the residents of Greenup County with a parade, reception, and banquet on June 2 for 51 years of medical service. Dr. Meadows, aged 87, has been active in the community for this entire period.——Dr. Robert L. Collins, Hazard, was presented

a community service plaque by the citizens of Perry County in appreciation of 38 years of service to the community and to the Frontier Nursing Service. Dr. Collins, who opened the first hospital in Hazard in association with the late Dr. A. M. Gross, has been active in the Perry County Health Department and in civic and community affairs.

MAINE

State Medical Association Moves.—The Maine Medical Association and its journal have moved from 142 High St., Portland 3, to the Dudley Coe Infirmary, Bowdoin College, Brunswick.

Postgraduate Course in Anesthesiology.—Members of the medical profession are welcome to attend the postgraduate educational program in anesthesiology being offered by the Maine General Hospital, Portland, in the house officers' quarters from 4 to 5 p. m. on the first and third Fridays of each month. On Nov. 18 the lecture will deal with intravenously given anesthesia.

MARYLAND

Society News.—The Radiological Section of the Baltimore City Medical Society will have as speaker Nov. 15, 5:30 p. m. at the Hopkins Club, Dr. H. S. N. Greene, Yale University School of Medicine, New Haven, Conn., who will discuss "Homologous and Heterologous Tumor Implants."

Dr. William Stone Named Dean.—Dr. William S. Stone, director of medical education and research at the University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, has been named dean of the school to succeed Dr. H. Boyd Wylie who retired July 1. Dr. Stone's new office will include the responsibilities of the director of medical education and research as well as those of the dean.

Personal.—Dr. Robert O. Scow, an investigator in basic research at the National Institutes of Health, Bethesda, who was recently selected as the Schering Scholar of the Endocrine Society for 1955, has gone to Argentina, where he will spend a year at the institute of Prof. B. A. Houssay in Buenos Aires. He will study the effects of hormonal and nutritional factors on the production, prevention, and cure of experimental diabetes.——Dr. Perry Franklin Prather, Hagerstown, deputy director of health in the state of Maryland, was recently appointed director of health to succeed Dr. Robert H. Riley, Baltimore, who, on March 18, submitted his resignation, effective Jan. 1, 1956.

MASSACHUSETTS

Society News.—At the annual meeting of the New England Diabetes Association the following officers were elected: Dr. Harry Blotner, Boston, president; Dr. Samuel B. Beaser, Boston, vice-president; Dr. C. Gabell Bailey, Boston, secretary; and Dr. Robert J. MacMillan, Boston, treasurer.

Hospital Teaching Clinic for Diabetic Patients.—Plans for construction of the world's first hospital teaching clinic for diabetic patients were recently announced by Dr. Elliott P. Joslin, Boston. The two-story, million-dollar clinic building, to be constructed as part of the New England Deaconess Hospital, will occupy the corner of Joslin and Pilgrim roads, opposite Harris Hall and the Deaconess Building. The basement will contain records, bookkeeping files, secretarial forces, secretaries' and residents' rest rooms, laboratory, and sterilizing, x-ray, and supply rooms. A part of the basement and most of the first floor will be rented by the Joslin Clinic. The second floor, devoted entirely to patients, will have rooms containing one, two, and four beds. Diagnostic offices will be arranged on both sides of the two interior corridors.

MICHIGAN

Society News.—New officers of the Michigan Allergy Society include Dr. Sidney Friedlaender, Detroit, president; Dr. Kenneth P. Mathews, Ann Arbor, vice-president; and Dr. E. Oskar Schreiber, Flint, secretary-treasurer.

Seminar on Schizophrenia.—In its seminar series the Association for Clinical and Research Studies, Ypsilanti State Hospital, will present Dr. John N. Rosen, New York, who on Nov. 18 will speak on the direct analytic treatment of schizophrenia. The seminar will be highlighted by clinical demonstrations of Dr. Rosen's techniques. The morning session will include a presentation of theoretical formulations.

Course in Industrial Audiology.—This course for industrial nurses, technicians, safety directors, and physicians, which began Nov. 8, has been instituted by the newly formed department of industrial medicine and hygiene, Wayne University College of Medicine, Detroit. Dr. Heinrich F. G. Kobrak, professor of industrial otolaryngology, and his staff are instructing the six-week course, which is meeting on Tuesdays, 6:30-8:30 p. m. at the medical school's new building, 1401 Rivard.

Medical Aspects of Civil Defense.—A symposium on the medical aspects of civil defense will be presented at the Sheraton-Cadillac Hotel, Detroit, Nov. 16 under the cosponsorship of the Lederle Laboratories Division of the American Cyanamid Company and the Michigan Office of Civil Defense. The purpose is to assist in the training of auxiliary medical aid to staff improvised hospital units and casualty care stations during time of national disaster. Subjects scheduled for discussion are: "Nuclear Weapons and Radioactive Fall-Out Patterns," "Chemical Warfare," "Biological Warfare," "Evacuation Policy," "Psychological and Sociological Consequences of Disaster," and "United States Public Health Service Responsibilities in Civil Defense." The speakers include Dr. James S. Tyhurst, assistant professor of psychiatry, McGill University Faculty of Medicine, Montreal; Dr. Leroy E. Burney, assistant surgeon general, U. S. Public Health Service, Washington, D. C.; and Col. William S. Moore, Office of the Surgeon General, Washington, D. C.

MINNESOTA

Meeting on Diabetes.—The Twin Cities Diabetes Association, a newly organized affiliate of the American Diabetes Association, will have Dr. Henry T. Ricketts, professor of medicine, University of Chicago School of Medicine, Chicago, as guest speaker at 6:15 p. m., Nov. 16, in Coffman Memorial Union, University of Minnesota, Minneapolis. Dr. Ricketts, former president of the American Diabetes Association, will consider "The Problem of Vascular Disease in Diabetes." Physicians are welcome. Information can be obtained through Dr. Wyman E. Jacobson, WA 6-6581, Minneapolis, or Dr. Marguerite Schwyzer, MI 8-3893, St. Paul.

Personal.—Dr. Frank H. Krusen, Rochester, and Dr. Edgar J. Huenekens, Minneapolis, have been appointed to the Minnesota State Board of Health by Governor Orville Freeman.——Dr. Fletcher A. Miller, a research fellow at the University of Minnesota Medical School, Minneapolis, has been granted the second Charles O. Finley Research Scholarship ($20,000). Dr. Miller is particularly interested in research on problems of cardiac arrest.——Dr. Leo G. Rigler, chief, department of radiology, University of Minnesota Hospitals, Minneapolis, has been appointed to the National Advisory Cancer Council. Dr. Rigler is on a year's leave of absence from the university, during which he is undertaking the establishment of a postgraduate program at the City of Hope Medical Center, Duarte, Calif.——Dr. Gustaf Arvid Hedberg, medical director of Nopeming Sanatorium, Nopeming, has been awarded the 1955 Dearholt medal by the Mississippi Valley Conference on Tuberculosis. The medal, named for the late Dr. Hoyt E. Dearholt of Milwaukee, is presented for outstanding service in tuberculosis control in the Midwest. Dr. Hedberg, assistant professor of medicine, University of Minnesota Medical School, Minneapolis, is area consultant in tuberculosis for the Veterans Administration.

MISSISSIPPI

Professors Appointed.—The University of Mississippi Medical Center, Jackson, has appointed as professor of obstetrics and gynecology and chairman of the department Dr. Michael Newton, formerly of the University of Pennsylvania School of Medicine, Philadelphia, and as professor of neurosurgery Dr. Orlando J. Andy of Johns Hopkins University School of Medicine, Baltimore.

MONTANA

State Medical Election.—The Montana Medical Association recently named Dr. Edward S. Murphy, Missoula, president-elect; Dr. John A. Layne, Great Falls, vice-president; Dr. Theodore R. Vye, Billings, secretary-treasurer (reelected). Dr. George W. Setzer, Malta, was installed as president.

NEW JERSEY

Alumni Dinner.—The Alumni Association of the Jersey City Medical Center will observe its eighth anniversary Nov. 16 at dinner at the Hotel Plaza, Jersey City, at which the main speakers will be Dr. Charles L. Brown and Merritte M. Maxwell, D.D.S., deans respectively of the new medical and dental schools of Seton Hall University, Jersey City.

Cancer Seminar.—The third cancer seminar will be held at the Hotel President, Atlantic City, Nov. 19-20, under the auspices of the American Cancer Society, New Jersey division, and the special committee on cancer control to the Medical Society of New Jersey. The program will open Saturday at 12:30 p. m. with a luncheon address by Dr. Joseph I. Echikson, Newark, on "The Cancer Control Program in New Jersey." At 2:30 p. m. "Radio Therapy Treatment of Cancer of the Uterus" will be presented by Dr. Milford D. Schulz, Boston, and at 3 p. m. "Differential Diagnosis of Abnormal Uterine Bleeding" by Dr. John Y. Howson, Philadelphia. "An Evaluation of the Lung Cancer Problem" will then be made by Dr. John L. Pool, New York (Diagnosis and Treatment); Dr. Charles S. Cameron, New York (Directions in Lung Cancer Research); and Dr. Alfred A. Gellhorn, New York (Clinical Investigative Trends in the Control of Leukemia and Lymphomata). The following program has been scheduled for Sunday:

Surgery vs. Radiotherapy in Breast Cancer, Lauren V. Ackerman, St. Louis.
Hormone Control in Breast Cancer, Olof H. Pearson, New York.
Analysis of Testicular Tumors, Frank J. Dixon, Pittsburgh.
Cancer Detection in Rural Group Practice, Caldwell B. Esselstyn, Hudson, N. Y.
Cancer Originating in the Head and Neck, Donald P. Shedd, New Haven, Conn.
Luncheon meeting, Miss Ethel J. Alpenfels, New York.
Cancer Research Today, George E. Moore, Buffalo.
Radioisotopes in Cancer, Benedict J. Duffy, Washington, D. C.
Conservatism vs. Radicalism in Colon Cancer, Isidor S. Ravdin, Philadelphia.
Adjuncts to Surgery in the Treatment of Cancer, Henry T. Randall, New York.

NEW YORK

Society News.—At the meeting of the Medical Society of the County of New York Nov. 17, 8:30 p. m., "Uterine Causes of Abortion and Premature Labour" will be discussed by Prof. T. N. A. Jeffcoate, professor of obstetrics and gynecology, University of Liverpool, England.——Dr. Walter T. Murphy, director of therapeutic radiology, Roswell Park Memorial Institute, Buffalo, will discuss "Radiation Therapy of Breast Carcinoma" before the Binghamton Academy of Medicine Nov. 15.

Conference on Aging.—The Capital District Conference on Aging, sponsored by the Albany County Department of Public Welfare, will be held Nov. 17 at the Ann Lee Home, Albany, with Dr. John J. Phelan, medical director of the home, as general chairman. A panel on medical services for the aging will be presented at 2:15 p. m. by Dr. Raymond Harris, assistant medical director, Ann Lee Home; Dr. Robert P. Whalen, medical administrator, Albany County Department of Public Welfare, Albany; and Dr. John J. Bourke, executive director, New York State Joint Hospital Survey and Planning Commission, Albany. Dr. John G. McKeon, attending physician of the home, will serve as moderator for the general discussion 3-4 p. m.

Dr. Robert E. Plunkett Honored.—Dr. Robert E. Plunkett, assistant commissioner for tuberculosis control, state department of health, Albany, was honored recently by the capital district chapter, American Society for Public Administration, which presented him with the Charles Evans Hughes award for 1954. Dr. Plunkett was cited for his "unusual dedication, administrative skill and concern for human values." Dr. Plunkett has been a U. S. delegate to international tuberculosis conferences, has served as special consultant in many parts of the world, and was special medical examiner with the U. S. Army Medical Corps from 1917 to 1920.

New York City

Harvey Lecture.—Joseph S. Fruton, Ph.D., professor of biochemistry, Yale University School of Medicine, New Haven, Conn., will deliver the third Harvey Lecture of the 1955-1956 series at the New York Academy of Medicine Nov. 17 on "Enzymic Hydrolysis and Synthesis of Peptide Bonds."

Tumor Clinic Conference.—Dr. Charles B. Ripstein, chief, divisions of general and thoracic surgery, Bronx Municipal Hospital Center, will present "The Surgical Treatment of Carcinoma of the Pancreas" at the tumor clinic conference in the Women's Pavilion, Harlem Hospital, Nov. 16, 10:45 a. m.

Course on Office Proctology.—Dr. Robert Turell and staff will give a course on office proctology Nov. 14-15 at the Mount Sinai Hospital, in affiliation with Columbia University. The course, designed to acquaint the clinician with the important proctologic conditions that lend themselves to office diagnosis and treatment, will include demonstration of all diagnostic and various therapeutic procedures. For information, address the Registrar for Postgraduate Medical Instruction at the Mount Sinai Hospital, Fifth Avenue and 100th Street, New York 29. The course will be repeated Feb. 20-21, 1956. The fee is $50.

Appoint Dr. McDermott Director of Research.—Dr. Walsh McDermott of Cornell University Medical Center, editor of the *American Review of Tuberculosis and Pulmonary Diseases*, has been appointed to succeed Dr. Esmond R. Long, Philadelphia, who retired July 1, as director of medical research of the National Tuberculosis Association. Dr. Floyd M. Feldmann, formerly assistant to the managing director, has been named medical director of the National Tuberculosis Association and will be associated with Dr. McDermott in the research program. Dr. McDermott, who was recently appointed to the Livingston Farrand Chair of Public Health and Preventive Medicine of Cornell University Medical College, has been with the college since 1937.

NORTH CAROLINA

Course on Trauma.—The University of North Carolina School of Medicine, Durham, offers a course on trauma, including burns, for general surgeons Nov. 17-18. A visiting speaker will be Dr. David M. Bosworth, director of orthopaedic surgery, St. Luke's Hospital, New York City. The program will include lectures, panel discussions, case presentations, and ward rounds.

Fellowships in Medicine.—The departments of medicine and preventive medicine, University of North Carolina School of Medicine, Chapel Hill, offer two fellowships in medicine, supported by the Commonwealth Fund, for the academic year starting July 1, 1956. The fellowships are designed primarily to provide experience in ambulatory medicine with emphasis on prevention and early diagnosis of disease and on the treatment of minor emotional problems and psychosomatic disorders. The annual stipend for each of the two fellowships is $3,600, tax free, plus $350 allowance for a dependent spouse and each dependent child. Applications should be sent before Dec. 1 and should indicate the candidate's background, interests, and future plans and include a small recent photograph. Address inquiries to: Dr. William L. Fleming, Director, General Clinic, North Carolina Memorial Hospital, Chapel Hill.

OHIO

Personal.—The Frank E. Bunts Educational Institute, affiliated with the Cleveland Clinic Foundation, announces that Dr. Charles L. Leedham assumed duties as director of education Sept. 1.

Society News.—The Academy of Medicine of Cincinnati (152 E. Fourth St.) will present "Drug Treatment of Hypertension" by Dr. George A. Perera, associate professor of medicine, Columbia University College of Physicians and Surgeons, New York, Nov. 15.

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Lectures on Neurology and Psychiatry.—The Cincinnati Society of Neurology and Psychiatry is presenting a series of evening lectures (8 p. m.) at the Cincinnati Sanitarium, 5642 Hamilton Ave., Cincinnati 24. The series opened Oct. 12 with "The Abortion Problem" by Dr. Harold Rosen, assistant professor of psychiatry, Johns Hopkins University School of Medicine, Baltimore. On Nov. 16 Dr. Henry A. Davidson, assistant superintendent, Essex County Overbrook Hospital, Cedar Grove, N. J., will discuss "Criminal Responsibility."

Fellowships in Industrial Medicine.—The Institute of Industrial Health, University of Cincinnati College of Medicine, is offering fellowships in industrial medicine to graduates of approved medical schools who have completed at least one year of internship. Two years are devoted to intensive academic and clinical study in industrial medicine, and the third year is spent in residency in an industrial medical department or in a comparable organization. Stipends for the first two years vary from $3,000 to $4,000, depending on marital status. In the final year a fellow is compensated by the organization in which he is completing his training. A one year certificate course, without stipend, is also offered to qualified applicants. Requests for information should be addressed to Secretary, Institute of Industrial Health, College of Medicine, Eden and Bethesda, Cincinnati 19.

PENNSYLVANIA

Course on Rehabilitation.—The University of Pennsylvania will offer a course, "Principles of Rehabilitation," at the Rehabilitation Center, University Hospital, on the following dates: Dec. 5-10, 1955; Feb. 6-11, 1956; April 2-7; and June 25-29. The course is open to physicians, registered nurses, occupational therapists, social workers, rehabilitation counselors, and others concerned with rehabilitation of the handicapped. Provision for granting a limited number of trainee stipends to eligible persons attending the course has been made by the U. S. Office of Vocational Rehabilitation. Applications for these stipends may be addressed to the Rehabilitation Center, Hospital of the University of Pennsylvania, Philadelphia 4.

Pittsburgh

Society News.—New officers of the Pittsburgh Pediatric Society include: Dr. William W. Briant, president; Dr. Robert R. Macdonald, vice-president; Dr. Bernard I. Michaels, secretary-treasurer.

Conferences on Industrial Medicine.—The 20th annual meeting of the Industrial Hygiene Foundation will be held at Mellon Institute, Pittsburgh, Nov. 16-17. On Wednesday at 9:30 a. m. the joint medical-chemical-toxicological conference will present a panel discussion, "Research Developments and Their Application in the Prevention of Occupational Disease." The afternoon session of the medical conference will open at 2 p. m. with "Mental Health as a Part of the Medical Program" by Dr. R. Christopher Leggo, Menlo Park, Calif., followed by a panel discussion, "Relationships Between the Medical Department and Management." For its afternoon session the joint engineering-legal conference will have a panel discussion, "Engineering and Legal Aspects of Management's Responsibility for Control of Industrial Hazards." On Thursday a general meeting will include presentation of "Graduate Education for Industry's Professional Personnel" by Dr. J. Roscoe Miller, president, Northwestern University, Evanston, Ill.

TEXAS

Personal.—Dr. Leigh J. Crozier, director of Hermann Hospital, Houston, was honored by the interns and residents of the hospital during the dinner meeting of the medical staff Sept. 23, when over 200 staff doctors were present. An engraved wrist watch was presented to him.

Society News.—Newly elected officers of the Lone Star State Medical Association include: Dr. Connie R. Yerwood, Austin, president; Dr. Joseph A. Chatman, Lubbock, president-elect; Dr. Peter G. Byrd, Beaumont, first vice-president; Dr. Wheatley C. Stewart, Odessa, second vice-president; Dr. Clarence C. B. Friday, Seguin, secretary; Dr. James M. Hilliard, Crockett, assistant secretary; and Dr. Henry D. Patton, Palestine, treasurer.

Health Unit Director Needed.—The Texas State Department of Health announces examinations for director, local health unit 1 A. The salary range is from $9,720 to $12,120; some large, metropolitan health departments may pay higher than this range from local sources. Currently these salaries are from $12,000 to $16,000 for entrance to the service. The minimum qualifications are (1) M.D. degree and one year's internship; (2) M.P.H. degree or certification by the American Board of Preventive Medicine; (3) two years of field experience after internship in general public health practice; (4) three years of additional experience in special training, teaching, or practice in preventive medicine and public health; and (5) licensure to practice medicine in Texas. For applications write: Merit System Council, 814 Littlefield Bldg., Austin, or Dr. Henry A. Holle, Commissioner of Health, Texas State Department of Health, 410 E. Fifth St., Austin.

VERMONT

Jobs for the Homebound.—A "pilot study" on methods of developing industrial employment for homebound handicapped persons is being conducted under the sponsorship of the Office of Vocational Rehabilitation in Washington, D. C., the American Foundation for the Blind, and National Industries for the Blind. Initial efforts will be concentrated on obtaining subcontract jobs from various industries. As the program develops, the possibility of producing items suitable for wholesale distribution and the manufacture of gift shop articles distinctive of Vermont will be explored. Headquarters of the industrial homework program have been established at 7 Langdon St. in Montpelier.

WISCONSIN

Grant for Cancer Research.—An institutional grant of $100,000 for cancer research was recently made by the American Cancer Society to the University of Wisconsin, Madison. Among projects to be supported are those concerned with the chemical composition of cells and cell particles, new methods of locating early cancers, trials of chemicals that might halt cancer, enzyme studies, studies of the origin of cancer in connection with protein and enzyme changes, chemicals that block cell growth, and analysis of nucleic acids that are cell constituents vital to cell growth.

State Medical Society Dedicates Offices.—The State Medical Society of Wisconsin dedicated its new offices at 330 E. Lakeside St., Madison, Oct. 15. Dr. William D. Stovall, Madison, past-president, presided. The remarks of the president were delivered by Dr. Ervin L. Bernhart, Milwaukee. Among those extending appreciatory remarks were Dr. Elmer Hess, Erie, Pa., President, American Medical Association; Dr. Gunnar Gundersen, La Crosse, Chairman, A. M. A. Board of Trustees; and Dr. George F. Lull, Chicago, A. M. A. Secretary and General Manager. Dr. Lowry H. McDaniel, Tyronza, Ark., Chairman, Section on General Practice, A. M. A., delivered the dinner address on "The Heart of Medicine."

HAWAII

Medical Association Plans for Centennial.—The Hawaii Medical Association invites members of the American Medical Association and their families to attend the centennial celebration in Honolulu April 22-29, 1956. The association, which secured its charter of incorporation from the Privy Council of King Kamehameha IV in 1856, plans to celebrate its centennial in Hawaiian style. In addition to scientific sessions with outstanding medical speakers from the United States, there will be a great pageant depicting the colorful history of medicine in the Islands, a luau (Hawaiian feast), and other events, with ample time for sight-seeing and relaxation. For information, write to the Hawaii Medical Association, 510 S. Beretania St., Honolulu 13, Hawaii.

GENERAL

Memorandums on Economic Poisons.—The National Agricultural Chemicals Association has prepared copies of the 1955 Revision of Clinical Memoranda on Economic Poisons, originally compiled by the U. S. Public Health Service Technical Development Laboratories. These memorandums, available without charge to physicians interested in the treatment of pesticide poisonings, may be obtained from the National Agricultural Chemicals Association, 1145 19th St., Washington, D. C.

Grants for Aeronautic Research.—At the annual meeting of the board of trustees and technical assistance board Dec. 16-17 in Washington, D. C., the Link Foundation will review requests for grants. Institutions and organizations interested in making application to the foundation should do so by Dec. 1. The primary purpose of the Link Foundation, whose office headquarters are at the Smithsonian Institution in Washington, D. C., is to make grants available to nonprofit institutions and associations for projects that advance education and training in aeronautics.

T. Duckett Jones Memorial Fund.—Friends of the late Dr. T. Duckett Jones have initiated the T. Duckett Jones Memorial Fund to advance his research objectives. The committee is presently of the opinion that research in rheumatic fever will be given priority by the fund's administrators. Depending on the amount received, a number of awards may be made to represent the philosophy and professional interests of Dr. Jones. Suggestions are welcomed by the committee. Contributions are tax exempt and should be sent to the T. Duckett Jones Memorial Fund, 525 E. 68th St., New York 21.

Association of Blood Banks.—The annual meeting of the American Association of Blood Banks will be held at the Palmer House, Chicago, Nov. 19-21. At the Saturday afternoon scientific session, Dr. R. R. A. Combs, department of pathology, University of Cambridge, England, will speak on the antiglobulin reaction and on Monday will open the afternoon session with "Detection of Platelet Antibodies by a New Method." Dr. Ruth Sanger, London, England, will present "Recent Blood Group Distinctions Between Certain Races" Sunday, 2 p. m. At the annual banquet Sunday, 7 p. m., Dr. Morris Fishbein, Chicago, will have as his subject "Blood—the Most Important Fluid." On Monday, luncheon discussion groups will consider: ACTH, cortisone, hydrocortone and meticortin and blood transfusion (tentative); red blood cell antigens and antibodies; blood storage; blood—patient insurance programs.

Meeting on School Health.—The 29th annual meeting of the American School Health Association will convene at the Hotel President and the Municipal Auditorium, Kansas City, Mo., Nov. 13-18. "The Association's Plan of Certification of Schools with Approved Programs for the Control of Tuberculosis" will be presented by Dr. Jay A. Myers, Minneapolis. Dr. Isaac P. Barrett, Fort Worth, Texas, president-elect, will preside at the second general session Thursday morning, when presentations will include "Advances in Communicable Disease Control" by Dr. Robert F. Korns, Albany, N. Y., and "Progress Against Chronic Disease in Children" by Dr. Thomas E. Shaffer, Columbus, Ohio. At the banquet Wednesday, 6:30 p. m., the William A. Howe award will be presented to Dr. Cyrus H. Maxwell, Assistant Director, Washington Office, American Medical Association.

Grants for Cancer Research.—The committee on growth of the National Academy-Research Council invites applications for grants for scholars in cancer research, offered by the American Cancer Society. These grants assist institutions in the support of young scientists during the critical early period of their careers as independent investigators. Grants are awarded for three years ($6,000 a year), with renewal for two additional years unless there are compelling reasons to the contrary. Applications should be submitted by institutions on behalf of candidates not later than Jan. 1. Application blanks may be obtained from the Executive Secretary, Committee on Growth, National Academy-Research Council, 2101 Constitution Ave., N. W., Washington 25, D. C.

Fellowship in Nutrition.—The National Vitamin Foundation invites persons with doctorate degrees in medicine or one of the biological sciences, interested in continuing training in nutrition, to become candidates for the second Russell M. Wilder Fellowship, which pays the recipient $4,500 the first year, $5,000 the second, and $5,500 the third year and is effective Jan. 1, 1956. Application forms are obtainable from the National Vitamin Foundation at 15 E. 58th St., New York 22. Applications must be accompanied by a letter from the executive officer of the institution where the work is to be done and by a letter from the head of the department under which the candidate is to work. The candidate must outline a program of investigation approved by his preceptor and give reasonable assurance that he will complete his fellowship and continue to work in the field of nutrition following the period covered by the fellowship. Applicants will be notified of action on or before Dec. 15.

Marriage-Career Views of Women Physicians.—The Barnard Alumnae Association of Barnard College, Columbia University, New York, recently sent a questionnaire regarding the feasibility of medical practice after marriage to 215 alumnae who are doctors and who took premedical courses at Barnard. Of the 124 alumnae who answered the questionnaire, 73% are combining their medical career with marriage and have an average of one and one-third children. Of the married doctors, 60% are putting into practice the theory that the marriage-career combination is more likely to succeed if the husband also is a doctor. One-fourth of the women replying specialize in pediatrics, one-eighth in internal medicine, another one-eighth in psychiatry, and the remaining half are general practitioners or are engaged in medical research, industrial medicine, school positions, and miscellaneous specializations. Asked whether their careers have been hampered because they are women, 91 replied "no," 22 "yes," and 8 "slightly." Only six answered "no" to the question, "If you had the choice to make over again, would you be a doctor?"

Cerebral Palsy Convention.—The United Celebral Palsy sixth annual convention is being held at the Hotel Statler, Boston, Nov. 11-13. The following Boston scientists will participate in the program:

Arthur M. Lassek, professor of anatomy, Boston University School of Medicine, Irreversibility of Motor Deficits Following Bilateral Cerebral Lesion.

Theodore H. Ingalls, associate professor of epidemiology, Harvard School of Public Health, Boston, Congenital Malformations in the Central Nervous System.

Paul I. Yakovlev, department of neurology, Harvard Medical School, Boston, Malformations of the End-Brain.

Bronson Crothers, professor of pediatrics, Harvard Medical School, Boston, Natural History of Cerebral Palsy and a special film project.

Betty Ben Geren, associate pathologist, Children's Cancer Research Foundation, Boston, Structure of the Neuron.

William T. Green, orthopaedic surgeon in chief, Children's Medical Center, Boston, Analysis of the Value of Surgical Procedures in the Treatment of Cerebral Palsy of the Spastic Type.

A symposium reassessing educational and clinical services for the cerebral palsied will be held Saturday afternoon with Dr. Arthur Miller, professor of education, Boston University, presiding.

Annual Meeting on Public Health.—The 83rd annual meeting of the American Public Health Association and 40 related organizations will convene in the Kansas City (Mo.) Municipal Auditorium Nov. 14-18. Dr. Herman E. Hilleboe, New York state commissioner of health, will deliver the presidential address Tuesday evening after the presentation of "Some Public Health Aspects of Medical Education" by Dr. Franklin D. Murphy, chancellor, University of Kansas, Kansas City. The general assembly will open at 10:30 a. m. Monday with a symposium on the theme of the entire meeting, "Where Are We Going in Public Health?" "Where Are We Going in World Health?" will be the topic for a symposium Wednesday evening. An address by Dr. Leonard A. Scheele, surgeon general, U. S. Public Health Service, "Mental Health—The New Frontier," is scheduled for Wednesday noon. On Thursday afternoon there will be a special session, "Practical Experience with Poliomyelitis Vaccine." Dr. Malcolm H. Merrill, Berkeley, Calif., will serve as moderator of the panel, with Drs. Robert D. Defries, Toronto, Canada,

Thomas Francis Jr., Ann Arbor, Mich., Jonas E. Salk, Pittsburgh, Leonard H. Scheele, Washington, D. C., and Hart Van Riper, New York, as participants. Thursday at 8:30 p. m., an address by Harry S. Truman will precede the presentation of the Lasker awards. Friday afternoon Dr. Hugh R. Leavell, Boston, will moderate a summary symposium on public health specialists.

Meeting on Cancer Cytology.—The Southern Society of Cancer Cytology will hold its annual meeting at the Shamrock Hotel, Houston, Texas, Nov. 13, under the presidency of Dr. H. Hudnall Ware Jr., Richmond, Va. The following program will be presented:

Value of Cytology in Diagnosis of Lung Cancer, Dewitt C. Daughtry, Miami, Fla.
Experience with Routine Prostatic Cytology in a Cancer Clinic, Lois I. Platt, Washington, D. C.
The Liaison Between Basic and Clinical Cytology, Milan J. Kopac, Ph.D., New York.
New Device for Cell Collection from Cervix Uteri; and Presentation of a New Scanning and Research Microscope, H. E. Nieburgs, Brooklyn, N. Y.
Value of Cytologic Methods in the Accidents of Early Pregnancy, Wayne S. Rogers, Miami, Fla.
Role of Cytology in Gynecological Research, J. Ernest Ayre and Homer L. Pearson, Miami, Fla.
Primary Biopsy Versus Cytology in Diagnosis of Cancer in Situ (round table), Ralph Jack, Miami, Fla., Chairman.
Developments in Cytology Training (Report of Educational Advisory Committee of the Society), Homer L. Pearson, Miami, Fla., Chairman.

Dr. Carlos A. Lamar, Miami, Fla., will be guest of honor at the dinner meeting (dress optional), 7 p. m., to which ladies are invited. Dr. Edmund V. Cowdry, director, Wernse Cancer Research Institute, Washington University School of Medicine, St. Louis, guest speaker, will discuss "The So-Called Precancer Cells."

Meetings on Preventive Medicine.—The Association of Teachers of Preventive Medicine will hold its 12th annual meeting Nov. 13 at the Kansas University Medical Center, Kansas City, Kan. Addresses will be delivered by Dr. William P. Shepard, New York, Chairman, A. M. A. Council on Industrial Health (Medicine and Industry—Some Expectations of Each) and Dr. Rodney R. Beard, San Francisco (Occupational Hygiene—a Vehicle for Teaching Preventive Medicine). At the dinner session, 7 p. m., at the Hotel Muehlebach, Kansas City, Mo., "The Future of Preventive Medicine in America" will be considered by Dr. Wilson G. Smillie, professor emeritus of public health and preventive medicine, Cornell University Medical College, New York City.——The second annual meeting of the American College of Preventive Medicine will convene at the Muehlebach Hotel, Kansas City, Mo., Nov. 16-17. The sessions will open Wednesday, 8 p. m., with "Opportunities, Responsibilities and Dreams of the College—A Challenge," by Dr. George A. Dame, Jacksonville, Fla., past-president, Dr. John W. R. Norton, Raleigh, N. C., president, and Dr. Charles F. Sutton, Springfield, Ill., president-elect. This presentation will be followed by a panel discussion, "Relationships of College Individual-State-National; Related Groups," by Dr. Edward H. Leveroos, Director, Division of Hospitals and Graduate Education, American Medical Association, Chicago, Dr. Vivian A. Van Volkenburgh, Albany, N. Y., and Dr. Ernest L. Stebbins, Baltimore. Thursday morning will be devoted to a report on the Cornell Auto Crash Injury Study and Results.

Meeting of Southern Medical Association.—The annual meeting of the Southern Medical Association will be held at the Shamrock Hotel, Houston, Texas, Nov. 14-17. The presidential address, "Values in Medicine," by Dr. Robert L. Sanders, Memphis, Tenn., Monday morning, will precede an address, "The Range of Loyalty," by Francis P. Gaines, Ph.D., president, Washington and Lee University, Lexington, Va. At the dinner dance Wednesday evening, Dr. W. Raymond McKenzie, Baltimore, will be installed as president. The section on gastroenterology has scheduled a panel discussion, "Relationship of Life Stress to Gastrointestinal Symptoms and Disease" for Monday afternoon; a panel discussion, "Medical Versus Surgical Management of Certain Esophageal Diseases" for Tuesday afternoon; and for Wednesday morning, in joint session with the section on surgery, a panel discussion, "Medical Versus Surgical Treatment of Gastric Ulcer." The sections on medicine and on pathology will offer a symposium on thyroid, with the cosponsorship of the Southeastern and South Central regional committees of the College of American Pathologists. The section on physical medicine and rehabilitation will have a symposium Tuesday morning on the rehabilitative management of the severely disabled, chronically ill, and aging, and on Wednesday morning a panel presentation on the effective rehabilitation of the disabled for actual employment. A geriatrics symposium Thursday morning will be followed by a round-table panel session. The annual golf tournament is scheduled for Tuesday and Wednesday at the Lakeside Country Club (grounds fee, $3). A postconvention tour of Mexico will leave Houston on the afternoon of Nov. 17. After three days in Mexico City, the party will be driven in private cars to Taxco and then to Acapulco. The main party will spend 10 days in Mexico, but a week-long extension will be available for those wishing to visit the more rural points of interest.

FOREIGN

Awards for Amateur Medical Films.—The annual prize for Medico-Surgical Cinema (about $290) and various other awards will be given during the last session of the course of "Actualités medico-chirurgicales" at the Faculté de Médicine de Paris in March, 1956. The awards will be made for only 16 mm. amateur films unpublished, not subsidized, and not produced by any laboratory or firm. The jury will consider the didactic value of the film as well as its cinematographic quality. Entries may be sound or silent films, in color or black and white. Applications should be sent soon. Films must be received no later than Feb. 20, 1956. For information contact La Presse Médicale, 120 Blvd. Saint Germain, Paris VIe.

Birth Rates.—According to a study of international birth trends by the Metropolitan Life Insurance Company, birth rates in most of Western Europe are receding from the peaks reached during the early postwar years. Exceptions to the general trend in Western Europe were noted in France and Norway, where the birth rate in 1954 was still appreciably above that recorded just before World War II. In England and Wales the rate rose from 15.9 per 1,000 population in 1945 to 20.6 in 1947 but fell to 15.2 by 1954—not much above the 1935-1939 average of 14.9. Austria, Denmark, Scotland, and Sweden had similar trends. Rates in Germany, Greece, Italy, and Portugal are now well below their prewar levels. In Japan the rate in 1954 was about one-third less than in 1935-1939, and in the Philippines the decline has been even more pronounced. However, in the United States and other English-speaking countries outside Europe (Canada, Australia, and New Zealand), birth rates have remained one-third or more above their prewar levels. The rate in the United States during 1954 (25.3 per 1,000 of population) was higher than for any prewar year since the early 1920's.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.

1955 Clinical Meeting, Boston, Nov. 29-Dec. 2.
1956 Annual Meeting, Chicago, June 11-15.
1956 Clinical Meeting, Seattle, Nov. 27-30.
1957 Annual Meeting, New York, June 3-7.
1957 Clinical Meeting, Philadelphia, Dec. 3-6.

NATIONAL MEDICAL PUBLIC RELATIONS CONFERENCE, Hotel Statler, Boston, Nov. 28. Mr. Leo F. Brown, 535 N. Dearborn St., Chicago 10, Director.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY, Palmer House, Chicago, Dec. 3-8. Dr. James R. Webster, 55 East Washington St., Chicago 2, Secretary.

AMERICAN ACADEMY OF OBSTETRICS AND GYNECOLOGY, Conrad Hilton Hotel, Chicago, Dec. 13. Dr. C. Paul Hodgkinson, 116 South Michigan Blvd., Chicago, Secretary.

AMERICAN ASSOCIATION OF BLOOD BANKS, Palmer House, Chicago, Nov. 19-21. Miss Marjorie Saunders, 3707 Gaston Ave., Dallas 10, Texas, Secretary.

AMERICAN COLLEGE OF PREVENTIVE MEDICINE, Kansas City, Mo., Nov. 16-17. Dr. T. Paul Haney, 521 North Boulder St., Tulsa, Okla., Secretary.

AMERICAN LEAGUE AGAINST EPILEPSY, Roosevelt Hotel, New York, Dec. 8. Dr. Peter Kellaway, Baylor University College of Medicine, Houston 25, Tex., Secretary.

AMERICAN PUBLIC HEALTH ASSOCIATION, Muehlebach Hotel and Municipal Auditorium, Kansas City, Mo., Nov. 14-18. Dr. Reginald M. Atwater, 1790 Broadway, New York 19, Executive Secretary.

AMERICAN RHEUMATISM ASSOCIATION, Interim Session, National Institutes of Health, Bethesda, Md., Dec. 9. Dr. Edward F. Hartung, 580 Park Ave., New York 21, Secretary.

AMERICAN SCHOOL HEALTH ASSOCIATION, Hotel President, Kansas City, Mo., Nov. 14-18. Dr. A. O. DeWeese, 515 East Main St., Kent, Ohio, Secretary.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASES, Hotel Roosevelt, New York, Dec. 9-10. Dr. Clarence C. Hare, 710 West 168th St., New York 32, Secretary.

EASTERN SECTION, AMERICAN FEDERATION FOR CLINICAL RESEARCH, Hotel Warwick and College of Physician's Building, Philadelphia, Dec. 2-3. Dr. Charles R. Shuman, Temple Univ. Hospital, Broad and Ontario Sts., Philadelphia 40, Chairman.

INDUSTRIAL HYGIENE FOUNDATION OF AMERICA, Mellon Institute, Pittsburgh, Nov. 16-17. Dr. C. Richard Walmer, Mellon Institute, Pittsburgh 13, Managing Director.

INTERSTATE POST GRADUATE MEDICAL ASSOCIATION OF NORTH AMERICA, Municipal Auditorium, Milwaukee, Nov. 14-17. Mr. Roy T. Ragatz, 207 Gay Bldg., Madison 3, Wis., Executive Director.

LOS ANGELES MIDWINTER MEDICAL CONVENTION, Biltmore Hotel, Los Angeles, Jan. 3-5. Dr. Paul D. Foster, 1925 Wilshire Blvd., Los Angeles 58, General Chairman.

MEDICAL SOCIETY EXECUTIVES CONFERENCE, Parker House, Boston, Nov. 27. Mr. H. Martin Baker, 1102 South Hillside, Witchita 17, Kansas, Secretary.

NEW ENGLAND HEALTH EDUCATION ASSOCIATION, Boston, Dec. 2. Miss Wyntha Tompkins, Middlesex Health Association, Essex, Mass., Secretary.

PUERTO RICO MEDICAL ASSOCIATION, Santurce, Dec. 7-11. Dr. Luis R. Guzman-Lopez, Box 9111, Santurce, Secretary.

RADIOLOGICAL SOCIETY OF NORTH AMERICA, Palmer House, Chicago, Dec. 11-16. Dr. Donald S. Childs, 713 E. Genesee St., Syracuse 2, N. Y., Secretary.

REGIONAL MEETINGS, AMERICAN COLLEGE OF PHYSICIANS:

CINCINNATI, Nov. 17. Dr. Charles A. Doan, Ohio State University College of Medicine, Columbus 10, Ohio, Governor.

BALTIMORE, Nov. 19. Dr. R. Carmichael Tilghman, 6 East Eager St., Baltimore 2, Governor.

VANCOUVER, B. C., Nov. 19. Dr. H. A. DesBrisay, 925 West Georgia St., Vancouver, B. C., Governor.

DETROIT, Dec. 3. Dr. H. Marvin Pollard, 1313 East Ann St., Ann Arbor, Mich., Governor.

HOT SPRINGS, ARK., Dec. 3. Dr. A. A. Blair, 100 S. 14th St., Ft. Smith, Ark., Governor.

WINSTON-SALEM, N. C., Dec. 8. Dr. Elbert Persons, Duke Hospital, Durham, N. C., Governor.

SOUTHERN MEDICAL ASSOCIATION, Shamrock Hotel, Houston, Texas, Nov. 14-17. Mr. V. O. Foster, 1020 Empire Bldg., Birmingham 3, Ala., Secretary-Manager.

SOUTHERN SOCIETY OF CANCER CYTOLOGY, Houston, Texas, Nov. 14-17. Dr. J. Ernest Ayre, 1155 N.W. 14th St., Miami, Fla., Secretary.

SOUTHERN SURGICAL ASSOCIATION, The Homestead, Hot Springs, Va., Dec. 6-8. Dr. George G. Finney, 2947 St. Paul St., Baltimore 18, Secretary.

SOUTHERN THORACIC SURGICAL ASSOCIATION, The Greenbrier, White Sulphur Springs, W. Va., Dec. 2-5. Dr. Hawley H. Seiler, 442 West Lafayette St., Tampa 6, Fla.

SOUTHWESTERN MEDICAL ASSOCIATION, Westward Ho Hotel, Phoenix, Ariz., Nov. 16-18. Dr. Celso C. Stapp, 800 Montana St., El Paso, Texas, Secretary.

WESTERN SURGICAL ASSOCIATION, Olympic Hotel, Seattle, Dec. 1-3. Dr. John T. Reynolds, 612 N. Michigan Blvd., Chicago 11, Secretary.

FOREIGN AND INTERNATIONAL

ALL INDIA MEDICAL CONFERENCE, Jaipur, India, Dec. 26-28. Dr. B. N. Consul, Association Bldg., S.M.S. Hospital Premises, Jaipur, India, Organizing Secretary.

CONFERENCE OF INTERNATIONAL UNION FOR HEALTH EDUCATION OF THE PUBLIC, Rome, Italy, Apr. 27-May 5, 1956. Mr. Lucien Viborel, 92 rue St. Denis, Paris 1er, France, Secretary-General.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LIMNOLOGY, Helsinki, Finland, July 26-Aug. 7, 1956. For information address: Dr. H. Luther, Snellmansgatan 16 C 36, Helsinki, Finland.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LOGOPEDICS AND PHONIATRICS, Barcelona, Spain, Sept. 3-7, 1956. Dr. J. Perello, Provenza 319, Barcelona 9, Spain, Secretary-General.

CONGRESS OF INTERNATIONAL SOCIETY OF HEMATOLOGY, Hotel Statler, Boston, Mass., U.S.A., Sept. 3-8, 1956. Dr. W. C. Moloney, 39 Bay State Road, Boston, Mass., U.S.A., Secretary.

CONGRESS OF INTERNATIONAL SOCIETY FOR RESEARCH ON ANESTHESIA, Miami Beach, Fla., U.S.A., Mar. 12-15, 1956. For information write: Dr. R. J. Whitacre, 13951 Terrace Road, Cleveland 12, Ohio, U. S. A.

CONGRESS OF LATIN SOCIETY OF OPHTHALMOLOGY, Madrid, Spain, April 24-28, 1956. For information address: Dr. Costi, Montalban 3, Madrid, Spain.

EUROPEAN CONGRESS OF ALLERGOLOGY, Florence, Italy, Sept. 12-15, 1956. Prof. Umberto Serafini, Instituto de Patologia Medica, Viale Morgagni, Florence, Italy, Secretary-General.

EUROPEAN CONGRESS OF CARDIOLOGY, Stockholm, Sweden, Sept. 10-14, 1956. Dr. Karl Erik Grewin, Sodersjukhuset, Stockholm, Sweden, General Secretary.

EUROPEAN SYMPOSIUM ON VITAMIN B12, Hamburg, Germany, May 1956. For information write: Doz. Dr. H. Bauer, Nervenklinik, Hamburg-Eppendorf, Germany.

INTER-AMERICAN CONGRESS OF CARDIOLOGY, Havana, Cuba, Nov. 4-10, 1956. For information address: Dr. Ramon Aixala, Apartado 2108, Havana, Cuba.

INTERNATIONAL ACADEMY OF PATHOLOGY, Cincinnati, Ohio, U. S. A., April 24-25, 1956. Dr. F. K. Mostofi, Armed Forces Institute of Pathology, Washington 25, D. C., U. S. A., Secretary.

INTERNATIONAL CONGRESS AGAINST ALCOHOLISM, Istanbul, Turkey, Sept. 10-15, 1956. For information address: International contre l'Alcoolisme, Case Gare 49, Lausanne, Switzerland.

INTERNATIONAL CONGRESS OF ANTHROPOLOGICAL AND ETHNOLOGICAL SCIENCES, Philadelphia, Pa., U. S. A., Sept. 2-9, 1956. Dr. William N. Fenton, National Research Council, Division of Anthropology and Psychology, 2101 Constitution Avenue, Washington 25, D. C., U. S. A., Secretary-General.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Cologne, Germany, Aug. 19-23, 1956. Mr. Murray Kornfeld, 112 East Chestnut St., Chicago 11, Illinois, U. S. A., Executive Director.

INTERNATIONAL CONGRESS OF ENTOMOLOGY, Montreal, Canada, Aug. 17-25, 1956. Mr. J. A. Downes, Science Service Bldg., Carling Ave., Ottawa, Ont., Canada, Secretary.

INTERNATIONAL CONGRESS OF GASTROENTEROLOGY, London, England, July 18-21, 1956. Mr. Hermon Taylor, London Hospital, White Chapel, London E.1, England, Honorable Secretary.

INTERNATIONAL CONGRESS FOR THE HISTORY OF SCIENCE, Florence and Milan, Italy, Sept. 3-10, 1956. Dr. M. L. Bonelli, Instituto di Ottica, Arcetri, Florence, Italy, Secretary-General.

INTERNATIONAL CONGRESS OF HYDATID DISEASE, Athens, Greece, Sept. 14-18, 1956. Prof. B. Kourias, Croix-Rouge Hellenique, 1 rue Mackenzie King, Athens, Greece, Secretary-General.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Madrid, Spain, Sept. 19-23, 1956. Dr. J. C. De Oya and Dr. J. Gimena, Hostaleza No. 90, Madrid, Spain, Secretaries.

INTERNATIONAL CONGRESS OF INTERNATIONAL COLLEGE OF SURGEONS, Palmer House, Chicago, Illinois, U. S. A., Sept. 9-13, 1956. Dr Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois, U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF NEO-HIPPOCRATIC MEDICINE, Montecatini, Terme, Italy, May 20-22, 1956. Dr. Valente, 41 Avenue Verdi, Montecatini Terme, Italy, Secretary-General.

INTERNATIONAL CONGRESS OF PAEDIATRICS, Copenhagen, Denmark, July 22-27, 1956. Professor P. Plum, Rigshospitalet, Copenhagen, Denmark, President.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Copenhagen, Denmark, August 20-24, 1956. Dr. B. Strandberg, Kobenhavns amts sygehus i Gentofte, Dept. of Rheumatology and Physical Medicine, Hellerup, Denmark, Honorable Secretary.

INTERNATIONAL CONGRESS OF PHYSIOPATHOLOGY OF ANIMAL REPRODUCTION AND ARTIFICIAL INSEMINATION, Cambridge, England, June 25-29, 1956. For information address: Dr. Joseph Edwards, Production Division, Milk Marketing Board, Thames Ditton, Surrey, England.

INTERNATIONAL CONGRESS OF RADIOLOGY, Mexico, D. F., Mexico, July 22-28, 1956. Dr. Jose Noriega, Tepic 126 (2e piso), Mexico, D. F. 7, Mexico, Secretary General.

INTERNATIONAL CONGRESS OF WORLD CONFEDERATION FOR PHYSICAL THERAPY, Hotel Statler, New York, New York, U. S. A., June 17-23, 1956. For information address: Miss Mildred Elson, American Physical Therapy Association, 1790 Broadway, New York 19, New York, U. S. A.

INTERNATIONAL GENETICS SYMPOSIUM, Tokyo and Kyoto, Japan, Sept 6-12, 1956. For information address: Secretary, International Genetics Symposium, Science Council of Japan, Ueno Park, Tokyo, Japan.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, Brussels, Belgium, July 29-Aug. 5, 1956. For information address: Prof. J. Reuse, Faculte de Medicine et de Pharmacie, 115 Boulevard de Waterloo, Brussels, Belgium.

INTERNATIONAL PROFESSIONAL UNION OF GYNECOLOGISTS AND OBSTETRICIANS, Madrid, Spain, Sept. 28-29, 1956. Dr. Jacques Courtois, 1 rue Racine, St-Germain-en-Laye (S and O), France, Permanent International Secretary-General.

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LATIN AMERICAN CONGRESS OF PATHOLOGY, Mexico, D. F., Mexico, Dec. 11-17. For information address: Laboratorio de Anatomia Patologica, Instituto N. de Cardiologia, Avenida Cuauhtemoc 300, Mexico 7, D. F., Mexico.

LATIN AMERICAN CONGRESS OF PHYSICAL MEDICINE, San Juan, Puerto Rico and Curacao, N.W.I., Jan. 29-Feb. 8, 1956. Dr. Cassius Lopez de Victoria, 176 East 71st St., New York 21, New York, U. S. A., Executive Director.

NORTH QUEENSLAND MEDICAL CONFERENCE, Cairns, North Queensland, Australia, June 25-30, 1956. Dr. W. R. Horsfall, P. O Box 672, Cairns, N.Q., Australia, Secretary.

PAN-AMERICAN ACADEMY OF GENERAL PRACTICE, San Juan, Puerto Rico and Curacao, N.W.I., Jan. 29-Feb. 8, 1956. Dr. Arturo Martinez, 54 East 72d St., New York 21, New York, U. S. A., Secretary.

PAN AMERICAN CONGRESS OF GASTROENTEROLOGY, Havana, Cuba, Jan. 20-27, 1956. For information address: Dr. Norberto M. Stapler, 1267 J. E. Uriburu, Buenos Aires, Argentine, S. A.

PAN AMERICAN CONGRESS OF OPHTHALMOLOGY, Santiago, Chile, S. A., Jan. 9-14, 1956. Dr. Rene Contardo, Huerfanos 930, Of. 74, Santiago, Chile, Secretary General.

PAN AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, San Juan, Puerto Rico, March 8-12, 1956. Dr. C. E. Munoz MacCormick, Apartado 9111, Santurce, Puerto Rico, Secretary General.

PAN AMERICAN MEDICAL WOMEN'S ALLIANCE, Santiago, Chile, March 6-13, 1956. For information address: Dr. Eva Cutright, 458 Beall Ave., Wooster, Ohio, U. S. A.

VENEZUELAN CONGRESS OF MEDICAL SCIENCES, Caracas, Venezuela, S. A., Nov. 18-26. Dr. A. L. Briceno Rossi, Apartado 4412, Ofic. del Este, Caracas, Venezuela, S. A., Secretary General.

WORLD CONGRESS ON FERTILITY AND STERILITY, Naples, Italy, May 18-26, 1956. For information address: Prof. G. Tesauro, S. Andrea della Dame, 19, Naples, Italy.

WORLD MEDICAL ASSOCIATION, Havana, Cuba, Oct. 9-15, 1956. Dr. Louis H. Bauer, 345 East 46th St., New York 17, New York, U. S. A., Secretary-General.

EXAMINATIONS AND LICENSURE

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY. *Written.* Various centers, July 26. *Oral.* St. Louis, Oct. 12-15. Sec., Dr. B. M. Kesten, One Haven Ave, New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* Chicago, Nov. 30-Dec. 1, *Subspecialties. Cardiovascular Disease.* Chicago, Nov. 30. The closing date for acceptance of application for gastroenterology was Feb. 1, and for cardiovascular disease the closing date was June 1. *Written.* Oct. 15, 1956. Final date for filing application is May 1. *Oral Examinations in 1956.* New Orleans, Feb. 7-10; Los Angeles, April 12-14; Chicago, June 7-9. Final date for filing application for these three oral examinations is Jan. 3. New York City, Sept. 21-25. Final date for filing application is April 1. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* New Haven, November. Oral examinations given in Spring and Fall. Final date for filing application for the Spring examination was October 1; for the Fall examination April 1. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Written Examination and submission of Case Reports. Part I.* Various locations in United States and Canada, and military centers outside of the Continental United States. Feb. 3, 1956. Final date for filing application was Oct. 1. *Oral and Pathological Examinations. Part II.* Chicago, May 11-20, 1956. Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written.* January 24-26, 1956. *Practical Examination.* San Francisco, June 18-21, St. Louis, Oct. 20-25. Applications for 1957 written examination must be filed before July 1, 1956. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Oral.* Jan. 26-27. Final date for filing application was Aug. 15. *Part I. Oral and written.* Various centers, April 1956. Final date for filing application is Nov. 30. Sec., Dr. Harold A. Sofield, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY. *Oral.* Montreal, Canada, May 6-10. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Washington, D. C., Dec. 2-4. Admin. Sec., Mrs. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION. *Parts I and II.* Chicago, June 16-17. Sec., Dr. Earl C. Elkins, 200 First St., S. W., Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY. *Entire Examination.* Buffalo, May 13-15. Final date for filing case reports is Jan. 1. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Certification in Public Health.* Kansas City, Mo., Nov. 10-12. Sec.-Treas., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore 5.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York City, December, Philadelphia, April 16-18, 1956. Sec., Dr. David A. Boyd, 102-110 Second Ave. S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Chicago, Dec. 4. Final date for filing applications for the fall examination was July 1. Candidates who will complete their training by Dec. 31 will be eligible to appear for this examination. Deadline for filing applications for the Spring 1956 examination is Jan. 1. Those candidates who will complete their training by June 30, will be eligible to appear at this examination. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part I.* Centers throughout the United States, in Europe and in the Far East, March 28. Closing date for the March examination is December 1. *Part II.* New York City, Nov. 14-15; St. Louis, Dec. 12-13; New Orleans, Jan. 16-17; Los Angeles, Feb. 13-14; San Francisco, Feb. 16-17; Durham, March 12-13; Boston, May 14-15 and Philadelphia, June 4-5. Sec., Dr. John B. Flick, 255 S. Fifteenth St., Philadelphia 2.

BOARD OF THORACIC SURGERY. *Written.* February 1956. Closing date for filing application is Dec. 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2, Mich.

MAGAZINE–TELEVISION REPORT

The following list of current medical articles in mass-circulation magazines and forthcoming network television programs on medical subjects is published each week only for the information of readers of THE JOURNAL. *Unless specifically stated, the American Medical Association neither approves nor disapproves of the articles and programs reported.*

TELEVISION

Saturday, Nov. 12

ABC-TV, 9 p. m. EST. "Tomorrow's Careers" will discuss the work of the dermatologist.

Monday, Nov. 21

NBC-TV, 11 a. m. to 12 noon EST. "Medical and Health News with Howard Whitman," a segment of the "Home" program.

NBC-TV, 9 p. m. EST. "Medic" presents "Candle of Hope," a dramatization of medicine's latest findings in the field of fertility.

ABC-TV, 9:30 p. m. EST. "Medical Horizons" takes its cameras to the Children's Hospital, University of Pittsburgh Health Center, to see how diabetic children are taught to live normal lives despite their affliction.

MAGAZINES

Cosmopolitan, November, 1955

"How Emotions Cause Unnecessary Surgery," by Alice Mulcahey

"Medical reports reveal that a shocking number of needless operations are performed each year because inner turmoil can produce bodily pain real and acute enough to fool you and your doctor." The author says that "too many surgeons are simply unaware that physical symptoms—and even laboratory readings which seem to demand an operation—can be produced by emotional problems."

Town Journal, November, 1955

"What to Do in Case of a Sudden Heart Attack," by John E. Eichenlaub, M.D.

The author tells about the two main types of heart attack—congestive failure and coronary attack—and describes the treatment used for each. An accompanying chart shows what to do if a heart attack hits suddenly.

GOVERNMENT SERVICES

AIR FORCE

Air Force Needs Career Physicians.—Air Force procurement figures indicate that the medical service has become increasingly attractive to physicians wishing to make a career of the military service. However, despite a significant increase in regulars, there are still a number of berths open. The Air Force Medical Service has become increasingly popular for reservists on active duty. At present requirements for reserve physicians on active duty have been met and further procurement has been temporarily suspended. This situation may change about March 1, 1956.

Physicians currently on duty with the Air Force number 3,190. Of these, 803 physicians are members of the regular component. The remainder are primarily reserve officers with an active duty retainability of about two years. About 45% of the physicians will be replaced through the Defense Department program for commissioning medical officers from the 1955 class of medical graduates who have unfulfilled military obligations. It is expected that the remaining 55% of the total FY 57 requirements for physicians will be supplied through Air Force recruitment of volunteers, both regular and reserve.

Award Distinguished Service Medal.—Brig. Gen. William J. Kennard was recently awarded the Distinguished Service medal by the chief of staff of the Air Force. The citation accompanying the award stated in part that General Kennard "distinguished himself by exceptionally meritorious service to the United States while serving in a position of great responsibility from 1 December 1951 to 14 October 1954. As Chief, Medical Branch and Senior Medical Officer of the North Atlantic Treaty Organization, Supreme Headquarters, Allied Powers in Europe, he . . . developed the organization of a Medical Committee which planned for the total health resources of the NATO nations. By his personal initiative, tact, and extensive knowledge of medical problems, General Kennard gained the assistance and cooperation of all countries concerned. In discharging his heavy responsibilities in such an outstanding manner, General Kennard has made a substantial contribution to the national security, and his actions reflect the highest credit upon himself and the United States Air Force."

Personal.—Col. Victor A. Byrnes, M. C., has been awarded the Legion of Merit. While assigned to the School of Aviation Medicine, Randolph Air Force Base, Texas, Colonel Byrnes conducted the original medical research to determine the extent to which an atomic flash would cause temporary blindness. As a result, the ability of personnel to discharge nighttime tasks, after being subject to the blinding effects of an atomic flash, was determined.——Col. Richard S. Fixott, M. C., was appointed chief of clinical medicine at the Air Force School of Aviation Medicine, Randolph Field, Texas, after completing a tour as surgeon of the Caribbean Air Command in the Canal Zone.

ARMY

General Gillespie Promoted.—Major Gen. James O. Gillespie, chief, professional division, office of the surgeon general, received the second star of this new rank in a ceremony in the surgeon general's office Oct. 20. General Gillespie was commissioned a first lieutenant in the Medical Officers Reserve Corps in 1925 and received his regular commission as a first lieutenant in 1927. In 1940 he was transferred to Manila, in the Philippine Islands, as chief of the medical service, Sternberg General Hospital. At the outbreak of the war with Japan, he became commanding officer of Sternberg.

General Gillespie was a prisoner of war of the Japanese for 40 months and was detained in prison camps in the Philippines, Formosa, Japan, and Manchuria until released in Mukden in August, 1945. In 1947 he completed postgraduate studies in internal medicine at the University of Minnesota and Harvard University.

In July, 1955, he was transferred to the office of the surgeon general as chief, professional services division. He has been awarded the Distinguished Service medal and the Legion of Merit. He is a diplomate of the American Board of Internal Medicine. One of his two sons is a senior medical student at Stanford University.

Personal.—Lieut. Col. Lee B. Grant, M. C., former chief, industrial hygiene and safety branch, preventive medicine division, Eighth Army, Far East Command, has been named deputy commander of the Army environmental health laboratory and chief of the occupational health division at the Army Chemical Center, Edgewood, Md.

PUBLIC HEALTH SERVICE

Length of Life Increases.—Average length of life in the United States has reached a record high of 68.8 years, a gain of more than 5 years since 1940, according to vital statistics compiled by the Public Health Service. The figures are based on death rates prevailing in 1953 and are contained in life tables published by the Department of Health, Education, and Welfare.

Women on the average live longer, outliving men by six years. The average lifetime expected for women at birth is 72.1 years, while the average for men is 66.1 years. This difference in the average duration of life for men and women has increased sharply since 1900, when females outlived males by an average of only two years.

White women at birth have an expectation of life of 72.9 years, compared to 66.8 years for white men. Nonwhite groups have a shorter average life—59.7 years for nonwhite men, and 64.4 years for nonwhite women. Although white persons outlive nonwhites by an average of eight years, the difference between the two groups has narrowed since 1900, when white persons lived about 15 years longer than nonwhites.

VETERANS ADMINISTRATION

Study of Veterans Training Program.—Severely disabled veterans of Korea are entering vocational rehabilitation training at a much greater rate than veterans with lesser disabilities. According to a VA study, one out of every five Korea veterans with disabilities rated at 60% or more have enrolled for training thus far, while only one out of 10 with disability ratings of less than 20% have taken training.

The VA study revealed also that the disabled trainees are aiming for high-level professional and managerial occupations in greater numbers than for any other type of jobs. So far 30,000 have entered training. The professional and managerial fields attracted 43% of trainees with orthopedic disabilities such as amputations; 40% of the blind; 52% of the hard-of-hearing; 54% of those with arrested tuberculosis; 47% of those with heart ailments; 43% of veterans who have had nervous or mental illnesses, and 40% of those with epilepsy. The average age of the disabled veterans was 25 at the time they entered training. The training program for disabled Korea veterans has been in operation for nearly five years and it still has a good number of years to go.

New Hospital Managers.—Dr. William J. McCarty, formerly manager of the VA Hospital at Vancouver, Wash., has been named manager of the VA Hospital at Wilkes-Barre, Pa., succeeding Dr. M. Herbert Fineberg, who will become manager of the VA Hospital in East Orange, N. J., succeeding Dr. Alfred P. Upshur, who will retire. Dr. Irving Eldridge, chief medical officer, VA Center, Bonham, Texas, will become manager of the VA Hospital at Fort Bayard to fill the vacancy created by the earlier transfer of Dr. Claude E. Carter to the VA Hospital in Butler, Pa.

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DEATHS

Levinson, Abraham ✦ Chicago; born in Linkovo, Russia, Aug. 25, 1888; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1911; received his bachelor of science degree from the University of Chicago in 1917; did postgraduate work at the University of Vienna in 1914, 1915, 1923, 1928, and 1930; professor of pediatrics, emeritus, at Northwestern University Medical School; professor of pediatrics at Cook County Graduate School of Medicine; specialist certified by the American Board of Pediatrics; vice-president of the Chicago Pediatric Society in 1935 and president in 1936; member of the American Academy of Pediatrics, Institute of Medicine of Chicago, American Association of the History of Medicine, Sigma Xi, and Phi Delta Epsilon; chairman of the committee on mental hygiene of the Illinois State Medical Society for many years; awarded a certificate of merit by the American Medical Association in 1932 for his scientific exhibit on cerebrospinal fluid in health and disease, and by the Illinois State Medical Society in 1936 for exhibit on experimental studies in cerebrospinal fluid and in 1940 for his exhibit on cerebral manifestations of the newborn; was given the Phi Lambda Kappa gold medal award for achievements in medical science in 1940 and the orator key of the History of Medicine Society of Tulane University School of Medicine in 1942; attending pediatrician at the Sarah Morris Hospital for Children, a unit of Michael Reese Hospital, where he was vice-president from 1933 to 1935, and chief of the pediatric department at the Mount Sinai Hospital, where he was vice-president from 1934 to 1936; attending pediatrician and chief of staff of the children's division of the Cook County Hospital; director of the Dr. Julian Levinson Research Foundation; his most notable achievements were in the field of pediatric neurology; described the Levinson phenomenon for the differential diagnosis between laryngeal diphtheria and laryngitis (1915); author of "Pediatric Nursing," translated into Hebrew in 1933, "Cerebrospinal Fluid in Health and Disease," and "The Mentally Retarded Child"; contributed chapters to systems of pediatrics; joint editor with Dr. I. A. Abt of "Pediatric Year Book" (1916-1920); died Sept. 17, aged 67, of acute myocardial infarction.

Gray, Howard Kramer ✦ Rochester, Minn.; born in St. Louis Aug. 28, 1901; Harvard Medical School, Boston, 1927; interned at the Robert Packer Hospital in Sayre, Pa.; professor of surgery at University of Minnesota Graduate School; since 1948 member of the board of governors of the Mayo Clinic; certified by the National Board of Medical Examiners; specialist certified by the American Board of Surgery; member of the American Surgical Association, Southern Surgical Association, Western Surgical Association, Society of Clinical Surgery, and the American Association of Thoracic Surgery; fellow of the American College of Surgeons; awarded the Navy Commendation ribbon for devotion to duty and Legion of Merit for exceptionally meritorious conduct during World War II; consultant at the Colonial and St. Mary's hospitals; awarded the honorary degree of doctor of science in 1949 from Lafayette College, Easton, Pa., and the same degree in 1954 by the University of Nebraska, Lincoln; in 1950 honored by appointment as the Lord Moynihan lecturer of the Royal College of Surgeons of England; joint author with Drs. Waltman Walters and James T. Priestley of "Carcinoma and Other Malignant Lesions of the Stomach"; was drowned in Lake Pepin Sept. 6, aged 54, while swimming to recover a dinghy that had become detached from his cabin cruiser.

Jacobson, Conrad ✦ Seattle; born in 1878; Johns Hopkins University School of Medicine, Baltimore, 1911; at one time on the faculty of the University of Minnesota Graduate School in Minneapolis; instructor of surgery at Harvard Medical School in Boston from 1912 to 1921; senior consultant in neurosurgery at the University of Washington Schools of Medicine and Dentistry; member of the founders group of the American Board of Surgery; consultant in surgery at the U. S. Public Health Service Hospital, Children's Orthopedic Hospital, and the King County Hospital; member of the American Association for the Surgery of Trauma and the American Association of Pathologists and Bacteriologists; past-president of the Seattle and Pacific Coast Surgical Societies; fellow of the American College of Surgeons; died in the Seattle General Hospital Sept. 21, aged 76, of cerebral embolism.

McCandlish, Howard Sheild ✦ Washington, D. C.; born in Washington Aug. 7, 1891; University of Virginia Department of Medicine, Charlottesville, 1917; interned at the Philadelphia General Hospital; later entered residency training at the New York Nursery and Childs Hospital in New York City; served during World War I; member of the Medical Society of the State of New York; formerly associate professor of clinical obstetrics and gynecology at Cornell University Medical College in New York City, where he was on the staff of the New York Hospital, French Hospital, and the Doctors Hospital; served on the staff of the North Country Community Hospital in Glen Cove, N. Y.; died in the Garfield Memorial Hospital Aug. 26, aged 64, of uremia and carcinoma of the prostate.

Sanborn, Harvey B. ✦ Rumford, R. I.; born March 8, 1881; Harvard Medical School, Boston, 1906; first president of the Rhode Island Society for Neurology and Psychiatry; served on the staff of the State Hospital for Mental Diseases in Howard; for many years practiced in Providence, where he served at one time as city physician, examining neuropsychiatrist for the U. S. Veterans Bureau, in the guidance department of the public schools, and on the staffs of the Butler Hospital, Charles V. Chapin Hospital, and the Rhode Island Hospital, where he died Sept. 10, aged 74, of cholelithiasis, arteriosclerotic heart disease, traumatic rupture of the stomach, and cerebral vascular accident.

Krell, Solomon ✦ New York City; born April 5, 1897; University and Bellevue Hospital Medical College, New York City, 1923; assistant clinical professor of medicine at the New York Medical College, Flower and Fifth Avenue Hospitals; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Heart Association; chairman of the board of censors of the Bronx County Medical Society; on the staffs of the Morrisania City Hospital, Home and Hospital of the Daughters of Jacob, and the Bronx Hospital, where he was chief cardiologist; died Sept. 5, aged 58, of coronary thrombosis.

Post, John James ✦ Nashville, Tenn.; born in Woodside, N. Y., April 26, 1893; Columbia University College of Physicians and Surgeons, New York City, 1919; member of the Nashville Academy of Medicine; medical examiner of draft board number two in Greensboro, N. C., in 1941 and 1942, and draft board number six in Nashville from 1942 to 1946; after World War II was cited by the government for work on the draft boards; at one time city health director of Greensboro, N. C.; formerly medical director of Life and Casualty Insurance Company; died in Vanderbilt University Hospital Aug. 12, aged 62, of emphysema.

File, Richard Cushing ✦ Decatur, Ill.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1942; member of the American Psychiatric Association; served during World War II; formerly on the staffs of the Peoria (Ill.) State Hospital and Pilgrim State Hospital in West Brentwood, N. Y.; at one time assistant superintendent and clinical director of Galesburg State Research Hospital in Galesburg; secretary and treasurer of the Decatur and Macon County Hospital staff; died in St. Luke's Hospital, Chicago, Aug. 30, aged 39, of glioma of the brain.

Anderson, Claude ✦ Fort Myers, Fla.; Jefferson Medical College of Philadelphia, 1927; served during World War II; accidentally drowned July 28, aged 55.

✦ Indicates Member of the American Medical Association.

Arko, Joseph Lawrence, Hibbing, Minn.; University of Minnesota Medical School, Minneapolis, 1939; served during World War II; member of the Minnesota State Medical Association; on the staff of the Hibbing General Hospital, where he died Sept. 9, aged 42, of osteosarcoma.

Atkins, George Hulings ✦ Philadelphia; Jefferson Medical College of Philadelphia, 1902; also a graduate in pharmacy; on the courtesy staff of Methodist Episcopal Hospital, where he died Sept. 3, aged 83, of carcinoma.

Backus, Glenn Russell ✦ Flint, Mich.; University of Michigan Medical School, Ann Arbor, 1930; president of the Michigan Pathological Society; specialist certified by the American Board of Pathology; member of the College of American Pathologists and the American Society of Clinical Pathologists; served during World War II; on the staffs of Hurley, McLaren, and St. Joseph hospitals; died in Marquette Sept. 5, aged 49, of acute pancreatitis.

Basile, Charles John ✦ Garden City, N. Y.; New York Medical College and Flower Hospital, New York City, 1937; certified by the National Board of Medical Examiners; specialist certified by the American Board of Orthopaedic Surgery; fellow of the American College of Surgeons; on the staffs of the Meadowbrook Hospital in Hempstead, Nassau Hospital in Mineola, and the Mercy Hospital in Rockville Centre, N. Y., where he died July 21, aged 43, of glomerular nephritis.

Bennion, Percival Hale ✦ White Plains, N. Y.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1902; member of the Minnesota State Medical Association; served on the staff of Midway Hospital in St. Paul; died June 30, aged 79, of a heart attack.

Boehning, Harold Henry, Abilene, Texas; Baylor University College of Medicine, Dallas, 1927; at one time a medical missionary in Korea; served on the staff of the Abilene State Hospital; died in Dallas Aug. 31, aged 61, of myocardial infarction.

Bonner, Kemp Plummer Battle ✦ Morehead City, N. C.; Medical College of Virginia, Richmond, 1905; chairman of the Carteret County Board of Commissioners; councilor from the First District from 1910 to 1921; director of the state bureau of maternity and infancy from 1922 to 1924; served as secretary of the state board of medical examiners, as vice-president of the Federation of State Medical Boards of the United States, and as mayor; on the staff of the Morehead City Hospital; died July 1, aged 72, of heart disease.

Branom, Le Roy ✦ Lincoln, Ill.; St. Louis University School of Medicine, 1919; past-president of the Logan County Medical Society and the Logan County Tuberculosis Association; on the staff of St. Clara's Hospital; died Sept. 11, aged 75, of fracture of the femur and cerebral hemorrhage.

Buikstra, Cyrus Renzo ✦ Evansville, Ind.; University of Kansas School of Medicine, Kansas City, 1926; on the staff of St. Mary's, Deaconess, and Welborn hospitals; died Aug. 25, aged 57, of coronary thrombosis.

Burt, Robert T., Clarksville, Tenn.; Meharry Medical College, Nashville, 1897; died Aug. 16, aged 83, of acute dilatation of the heart and arteriosclerosis.

Camp, Raymond Short ✦ Gainesville, Fla.; Emory (Ga.) University School of Medicine, 1942; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; on the staff of the Alachua General Hospital; was shot and killed Aug. 29, aged 36.

Campbell, Perry Alfred ✦ Richmond, Ind.; Indiana University School of Medicine, Indianapolis, 1940; served as an intern and resident at the Methodist Hospital in Indianapolis; formerly a resident at St. Luke's Hospital in Chicago; on the staff of the Reid Memorial Hospital; died July 26, aged 52, of coronary disease.

Cleaves, Harry Franklin ✦ Seattle; Tufts College Medical School, Boston, 1908; formerly county health officer; died Sept. 15, aged 77, of an accidental fall.

Conahan, Frank Joseph ✦ Bethlehem, Pa.; Medico-Chirurgical College of Philadelphia, 1915; past-president of the Northampton County Medical Society; served during World War I; formerly county medical director; on the staff of St. Luke's Hospital, where he died Sept. 10, aged 65, of cerebral thrombosis.

Conterman, Frank Beeby ✦ Ilion, N. Y.; Syracuse University College of Medicine, 1910; past-president of the Herkimer County Medical Society; from 1916 to 1951 health officer for Ilion and from 1932 to 1951 for the town of German Flatts and the town of Columbia; member of the board of managers of the Pine Crest Sanatorium in Salisbury Center; on the staff of the Ilion Hospital, where he died Sept. 1, aged 66, of cerebral hemorrhage.

Cordray, Palmer Lloyd ✦ Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1923; on the staff of the Mount Carmel Hospital; died Sept. 9, aged 65, of heart disease.

Cornell, Joseph H. ✦ Schenectady, N. Y.; Albany (N. Y.) Medical College, 1920; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; past-president of the Schenectady County Medical Society; on the staff of the Ellis Hospital; died Aug. 26, aged 59, of acute coronary thrombosis.

Cornthwaite, Miles J., Ballston Spa, N. Y.; Albany (N. Y.) Medical College, 1905; school physician; town of Milton health officer; chief of staff, Benedict Memorial Hospital; died Aug. 26, aged 76, of subacute endocarditis.

Crabtree, Peter ✦ San Diego, Calif.; University of Michigan Medical School, Ann Arbor, 1937; at one time on the faculty of his alma mater; specialist certified by the American Board of surgery; fellow of the American College of Surgeons; served during World War II; consultant in surgery at the U. S. Naval Hospital; served on the staffs of the San Diego County General Hospital, Children's Hospital, Quintard Hospital, and the Mercy Hospital, where he died Sept. 8, aged 42, of carcinoma of the bladder.

Davis, Henry Levi ✦ San Francisco; Tufts College Medical School, Boston, 1914; died July 6, aged 65, of carcinoma of the pancreas.

Denman, Peyton Roland ✦ Houston, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1903; fellow of the American College of Surgeons; served during World War I; at various times member and past-president of the staff of the Memorial Hospital and on the staffs of the Jefferson Davis Hospital, where he was at one time on the executive board, and the Hermann Hospital, where he died Aug. 16, aged 76, of carcinoma of the prostate.

Dwyer, John Robert ✦ Council Bluffs, Iowa; John A. Creighton Medical College, Omaha, 1912; formerly on the faculty of his alma mater; practiced in Omaha, where he was on the staffs of St. Joseph's Hospital and St. Catherine's Hospital, where he died July 26, aged 72, of hepatic cirrhosis.

Earl, William Henry, Cottage Grove, Ore.; University of Kansas School of Medicine, Kansas City, 1930; served as city health officer; on the staff of the Cottage Grove Hospital; died in Portland Aug. 19, aged 50, of subdural hematoma.

Ellis, William Wesley ✦ Marceline, Mo.; Keokuk (Iowa) Medical College, 1895; died Sept. 3, aged 81, of diabetes mellitus.

Foster, Thomas Jefferson, De Soto, Ill.; St. Louis University School of Medicine, 1903; served as principal of the Ewing High School in Ewing, where he was professor of Latin and Greek at Ewing College; for many years had staff privileges at St. Mary's and Decatur and Macon County hospitals in Decatur, and the Holden Hospital in Carbondale, where he died Sept. 14, aged 84, of myocarditis.

Frederickson, John Wardell, Oklahoma City; University of Oklahoma School of Medicine, Oklahoma City, 1947; resident at the University Hospitals and the Veterans Administration Hospital; died Sept. 21, aged 31.

Gama, Pablo Jose, Los Angeles; Instituto Literario y Científico (Escuela de Medicina de San Luis Potosi) San Luis Potosi, Mexico, 1906; died in the Good Samaritan Hospital Sept. 22, aged 70, of cerebral hemorrhage.

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Gardner, Joseph Leonard ✦ Sulphur Springs, Ga.; Birmingham Medical College, 1913; killed Aug. 28, aged 66, when his automobile was struck by a truck.

Gerns, Theodore ✦ Canton, Ohio; Universität Heidelberg Medizinische Fakultät, Baden, Germany, 1904; on the staffs of the Aultman, Mercy, and Timken-Mercy hospitals; served with the German Army during World War I; died Aug. 30, aged 74, of cancer of the prostate.

Grisier, Otto Woodson ✦ Captain, U. S. Navy, retired, Santa Barbara, Calif.; Harvard Medical School, Boston, 1913; appointed an assistant surgeon in the Navy Sept. 6, 1917; promoted to captain in 1942; retired Sept. 1, 1946, by reason of physical disability; served during World Wars I and II; fellow of the American College of Surgeons; died in the Cottage Hospital Sept. 11, aged 68, of lobar pneumonia.

Guild, Carl Holmes ✦ Shidler, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1918; served during World War I; for many years on the local school board; a director of the Shidler State Bank; died Sept. 15, aged 67.

Hall, Gilbert Hoke ✦ Tulsa, Okla.; University and Bellevue Hospital Medical College, New York City, 1901; died in the Hillcrest Memorial Center Sept. 17, aged 83, of coronary thrombosis.

Hamilton, William Franklin ✦ Van Nuys, Calif.; University of Louisville (Ky.) Medical Department, 1911; died Aug. 1, aged 71, of congestive heart disease.

Harris, Sigel Clance, Chicago; University of Illinois College of Medicine, Chicago, 1925; died Sept. 8, aged 69.

Kelly, Blair ✦ Ferris, Ill.; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1902; past-president of the Hancock County Medical Society; on the staff of the Memorial Hospital in Carthage; died in LaHarpe Aug. 23, aged 79, of coronary thrombosis.

Kincaid, Robert Lee, Crowell, Texas; Memphis (Tenn.) Hospital Medical College, 1900; president and director of the Crowell State Bank; died Sept. 12, aged 81, of injuries received in an automobile accident.

Kramer, Henry Frederick ✦ Brooklyn, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1907; past-president of the New York Gastroenterological Society; on the staffs of the Brooklyn and Norwegian hospitals; died in New Milford, Conn., Sept. 12, aged 69, of cerebral accident.

Lacy, Joseph Barkley ✦ Nathalie, Va.; Medical College of Virginia, Richmond, 1905; died in Richmond Aug. 12, aged 83.

Lang, Dorothy Mary, White Plains, N. Y.; University of Vermont College of Medicine, Burlington, 1924; specialist certified by the American Board of Pediatrics; fellow of the American Academy of Pediatrics; member of the American Psychosomatic Society and the American Academy of Allergy; attending pediatrician to the Grasslands Hospital in Valhalla and the White Plains Hospital; consulting pediatrician to the Phelps Memorial Hospital in Tarrytown; died in the Greenwich (Conn.) Hospital Sept. 18, aged 56, of carcinoma of the liver.

Levick, Julius Ernest ✦ Houston, Texas; University of Manitoba Faculty of Medicine, Winnipeg, Manitoba, Canada, 1923; served during World War II; on the staff of the Veterans Administration Hospital; died Aug. 26, aged 56, of myocardial infarction and coronary occlusion.

Low-Beer, Bertram V. A. ✦ San Francisco; born Dec. 11, 1900; Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, 1924; professor of radiology at the University of California Medical School; specialist certified by the American Board of Radiology; member of the Radiological Society of North America; fellow of the American College of Radiology; author of "Clinical Uses of Radioactive Isotopes"; died in the University of California Hospital Sept. 25, aged 54, of myelogenous leukemia and toxic hepatitis.

Lynch, Russell Earl ✦ St. Clair Shores, Mich.; University of Michigan Medical School, Ann Arbor, 1923; an associate member of the International College of Surgeons; past-president of the Macomb County Medical Society; mayor of the city of Center Line from 1934 to 1940; served on the staffs of the Holy Cross Hospitals in Detroit, and St. Joseph Hospital in Mount Clemens, where he was past-president of the staff; died Aug. 14, aged 54, of coronary thrombosis.

McCown, Percy Edward ✦ Indianapolis; Indiana University School of Medicine, Indianapolis, 1908; specialist certified by the American Board of Urology; member of the American Urological Association; on the staffs of the Indianapolis General, Methodist, and St. Vincent's hospitals; died in Taunton, Mass., Aug. 8, aged 71, of cerebral hemorrhage.

McCoy, John C., Buckhannon, W. Va.; Maryland Medical College, Baltimore, 1905; county health officer; school doctor; on the staff of the Elizabeth Coplin Leonard Memorial Hospital; died Sept. 7, aged 79, of arteriosclerosis.

McFarland, Samuel Byrd, La Jolla, Calif.; Kansas City (Mo.) Homeopathic Medical College, 1901; at one time on the staff of the Veterans Administration Facility, Fort Miley, San Francisco; died Sept. 2, aged 80.

McGuffie, Charles Robert, Woodruff, W. Va.; Bennett Medical College, Chicago, 1915; died Sept. 8, aged 73.

McNaugher, Samuel ✦ Pittsburgh; University of Pennsylvania Department of Medicine, Philadelphia, 1889; an associate member of the American Medical Association; on the staff of the Allegheny General Hospital; died Aug. 29, aged 92, of arteriosclerosis.

Meyers, Jerome, New York City; Albany (N. Y.) Medical College, 1907; member of the Medical Society of the State of New York and the American Public Health Association; served as senior district health officer at the Mott Haven Health Center; at one time on the faculty of his alma mater; died in the Doctor's Hospital Sept. 11, aged 72, of coronary thrombosis.

Miltimore, Edward, New York City; Albany (N. Y.) Medical College, 1905; member of the Medical Society of the State of New York; died in September, aged 74.

Moennighoff, Fritz Joseph ✦ Monett, Mo.; Kansas City (Mo.) Medical College, 1905; served during World War I; on the staff of the St. Vincent Hospital; died Sept. 7, aged 74, of cerebral hemorrhage.

Moore, John Morgan ✦ San Francisco; University of California Medical School, San Francisco, 1932; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; at one time second vice-president of the San Francisco County Medical Society; on the staffs of the Hahnemann Hospital and the Children's Hospital, where he was medical director of the outpatient department, and where he died Sept. 6, aged 50, of myocardial infarction and coronary occlusion.

Mutter, Alfred Aloysius, Essex Fells, N. J.; University of Louisville (Ky.) Medical Department, 1905; an associate member of the American Medical Association; practiced in Kearny for many years, serving on the staff of the West Hudson Hospital, where he died Sept. 26, aged 71, of arteriosclerotic heart disease.

Nelson, Leo Arthur ✦ Dallas, Texas; State University of Iowa College of Medicine, Iowa City, 1916; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; on the staffs of the Dallas Medical and Surgical Clinic-Hospital, Baylor University Hospital, and St. Paul's Hospital; died Aug. 18, aged 66, of arteriosclerosis.

Niell, Arthur Harry, Clover, S. C.; University of Virginia Department of Medicine, Charlottesville, 1912; died Aug. 25, aged 71, of carcinoma of the lung.

Nipple, Frederic E. ✦ Mulberry, Kan.; University Medical College of Kansas City, Mo., 1906; died in Mount Carmel Hospital in Pittsburg Sept. 1, aged 80, of chronic intestinal nephritis.

Nowak, Stanley Alfred, Buffalo; University of Buffalo School of Medicine, 1927; interned at the Sisters of Charity Hospital, where he died Sept. 12, aged 51, of myocardial fibrosis.

Nowicki, Joseph Aloisius ✦ Detroit; University of Buffalo School of Medicine, 1912; served during World War I; on the staff of the Grace Hospital; died in the Redford Branch of the Receiving Hospital Aug. 24, aged 66, of fracture of the skull when his automobile was struck by a train.

Nunnally, William Ord ✦ Fairmont, W. Va.; Temple University School of Medicine, Philadelphia, 1942; interned at Methodist Hospital in Philadelphia; killed in an airplane accident Sept. 4, aged 37.

Oliver, Hudson Jones Jr., New York City; Howard University College of Medicine, Washington, D. C., 1913; member of the Medical Society of the State of New York; served during World War I; at one time associated with the Harlem Hospital; died in the Veterans Administration Hospital Sept. 20, aged 66, of cancer.

Onstine, Warner Abram ✦ Taos, N. Mex.; Ohio Medical University, Columbus, 1896; on the staff of the Holy Cross Hospital; died Sept. 7, aged 83, of coronary thrombosis.

Overton, Marvin Cartmell Sr. ✦ Lubbock, Texas; University of Louisville (Ky.) Medical Department, 1902; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; past-president of the Lubbock-Crosby Counties Medical Society; on the staff of the Methodist Hospital; author of "Your Baby and Child"; died Sept. 1, aged 77, of myeloid metaplasia.

Page, Claude Weston ✦ McKees Rocks, Pa.; Jefferson Medical College of Philadelphia, 1907; on the staffs of the Ohio Valley and St. John's hospitals; died Aug. 20, aged 72, of arteriosclerotic heart disease and coronary thrombosis.

Peck, Robert Ellsworth ✦ Dunbarton, N. H.; Yale University School of Medicine, New Haven, Conn., 1893; for many years practiced in New Haven, Conn., where he was on the staff of the Grace-New Haven Community Hospital; died in the Moore General Hospital, Goffstown, N. H., July 6, aged 88, of carcinoma.

Phelan, Emma ✦ Imperial, Mo.; St. Louis College of Physicians and Surgeons, 1909; at one time vice-president of St. Louis Medical Society; served on the staffs of the St. Louis County Hospital in Clayton and the Deaconess Hospital and St. John's Hospital in St. Louis, where she died Aug. 21, aged 79, of myocardial decompensation.

Pierce, Franklin Duane, Buffalo; Syracuse University College of Medicine, 1904; died Sept. 16, aged 78, of arteriosclerotic heart disease.

Reckefus, Charles Halwadt Jr. ✦ Philadelphia; Jefferson Medical College of Philadelphia, 1893; member of the honorary staff at Lankenau Hospital, where he died Sept. 12, aged 84, of carcinoma of the pancreas.

Richards, Joseph Francis, Bellevue, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1917; died June 5, aged 61, of heart disease.

Roberts, William Humes ✦ La Jolla, Calif.; Cooper Medical College, San Francisco, 1894; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology and the American Laryngological, Rhinological and Otological Society; fellow of the American College of Surgeons; an associate member of the American Medical Association; died Sept. 18, aged 83.

Robinson, James Lee ✦ Lieutenant colonel, U. S. Army, retired, Los Angeles; Johns Hopkins University School of Medicine, Baltimore, 1908; entered the regular Army in 1911; retired May 9, 1920; became lieutenant colonel June 21, 1930; served during World War I; died in the Hollywood Presbyterian Hospital Sept. 15, aged 71, of heart disease.

Ruff, Adolph ✦ Philadelphia; Temple University School of Medicine, Philadelphia, 1908; died Sept. 10, aged 72, of cerebral hemorrhage.

Sanders, William A., Antlers, Okla.; Eclectic Medical University, Kansas City, Mo., 1911; died Aug. 31, aged 69, of cancer.

Segal, Myer, Camden, N. J.; Medico-Chirurgical College of Philadelphia, 1912; died in the University Hospital, Philadelphia, Sept. 8, aged 65.

Senor, Samuel David ✦ St. Joseph, Mo.; Northwestern Medical College, St. Joseph, 1889; from 1889 to 1906 taught general anatomy, anatomy of the central nervous system, and histology at Central, Northwestern, and Ensworth medical schools; died Sept. 21, aged 88, of cerebral hemorrhage.

Shannon, James Herbert, Washington, Pa.; Harvard Medical School, Boston, 1901; died in the Mercy Hospital, Pittsburgh, Aug. 5, aged 79, of bronchopneumonia and arteriosclerotic heart disease.

Snearly, George Earl, Houston, Texas; Chicago College of Medicine and Surgery, 1906; served during World War I; died in the Heights Hospital Sept. 14, aged 74, of coronary thrombosis with infarction.

Souders, John Cloyd ✦ Rock Island, Ill.; State University of Iowa College of Medicine, Iowa City, 1904; past-president of the Rock Island County Medical Society; on the staff of St. Anthony's Hospital in Rock Island and the Lutheran Hospital in Moline; died Aug. 23, aged 82, of cancer.

Sprinkle, Davis Lee ✦ Dallas, Texas; Baylor University College of Medicine, Dallas, 1930; member of the Radiological Society of North America; died in the Baylor University Hospital Aug. 27, aged 65, of a heart attack.

Stanley, Francis Guy ✦ Beverly, Mass.; Harvard Medical School, Boston, 1909; served as chief surgeon at the Lynn and Union hospitals in Lynn; formerly city physician and school committeeman; died Aug. 24, aged 80, of coronary arteriosclerosis.

Supple, William Raymond ✦ Cambridge, Mass.; Harvard Medical School, Boston, 1919; veteran of World War I; on the staff of the Charles Choate Memorial Hospital in Woburn, and Chester, Mount Auburn, and Sancta Maria hospitals; died Aug. 24, aged 62, of coronary disease.

Vaughan, James Maurice, Camden, N. J.; Howard University College of Medicine, Washington, D. C., 1914; member of the Medical Society of New Jersey; died June 17, aged 65, of a heart attack.

Wallin, Mathilda K. ✦ Elmsford, N. Y.; Woman's Medical College of the New York Infirmary for Women and Children, New York City, 1893; an associate member of the American Medical Association; died in Dobbs Ferry (N. Y.) Hospital Sept. 19, aged 97, of arteriosclerotic heart disease, pneumonia, and hypertension.

Weidlein, Floyd Henry, Palisade, Colo. (licensed in Colorado in 1916); died in Grand Junction Aug. 12, aged 67, of cerebrovascular arteriosclerosis.

Wilcox, Clarence Robert ✦ Jacksonville, Fla.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1904; on the staffs of the Duval Medical Center, St. Vincent's, and St. Luke's hospitals; died Aug. 2, aged 76.

Wood, William Patton ✦ Strawberry Plains, Tenn.; University of Tennessee Medical Department, Nashville, 1894; past-president of the Knox County Medical Society and the Tennessee State Medical Association; a founder of the Fort Sanders Hospital, where he was on the staff for many years; died Sept. 3, aged 86, of arteriosclerotic heart disease.

Woodall, John Burleson, Port Arthur, Texas; Baylor University College of Medicine, Dallas, 1936; died in an automobile accident Aug. 30, aged 49.

Wright, John Alexander, Doswell, Va.; University College of Medicine, Richmond, 1898; surgeon for the Chesapeake and Ohio Railroad; died Sept. 2, aged 79, of cerebral thrombosis.

Yeisley, Carl Jay ✦ Bakersfield, Calif.; University of Michigan Medical School, Ann Arbor, 1920; member of the American Academy of General Practice; past-president of the Ottawa County Medical Society; served during World War I; formerly practiced in Port Clinton, Ohio, where he was associated with the H. B. Magruder Memorial Hospital; died Aug. 3, aged 61.

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FOREIGN LETTERS

DENMARK

Danish Medical Association.—The annual report of the Danish Medical Association describes the many activities it undertakes on behalf of its 5,417 members. It provides locum tenens (591 last year), negotiates the sales of practices, helps to arrange partnerships, issues certificates of proficiency to chiropodists and experts in speech defects, and arbitrates over disputes its members may have with other bodies. Under the national health insurance scheme a distinction is made between the drugs that can or cannot be prescribed at a reduced rate, and the association therefore has to deal every year with a crop of applications from the vendors of certain drugs anxious to have them put on the privileged list. Insurance clubs sometimes complain that physicians have erred in prescribing expensive drugs not on this privileged list, and, though most such complaints are justified, it is evident that the overwhelming majority of the medical profession obey both the spirit and the letter of the law in this respect. The few black sheep in the association's flock are dealt with gently but firmly, and, though none is mentioned by name in this report, enough is said about them to indicate how hard the path is made for the transgressor. An example is given of the slovenly drafting of a certificate that read: "According to the information available to me Mr. Doe has been unfit for work on account of pain in his back." The author of this noncommittal statement had added insult to injury by writing it on a plain sheet of paper instead of on the official form. Another physician repeatedly guilty of drafting slovenly certificates is warned that his expulsion from the association will be considered on the next occasion. Even trivial complaints have to be examined conscientiously before they are dismissed as, for example, when the author of an article complained that the editor of *Ugeskrift for læger* had refused to publish it. After the editor had given the association his excellent reasons for rejecting this article, the complainant was informed that, if the editor had no right to refuse an article sent him, the journal might as well dispense with an editor altogether.

Psittacosis (Ornithosis).—Volkert and Christensen in the *Danish Medical Bulletin* (vol. 2, no. 2, 1955) report routine complement fixation tests on several hundred patients, most of whom had atypical pneumonia. Among them, 94 were found to be serologically positive with titers of 1:30 to 1:960. Of 20 patients whose occupations included the handling of birds, 18 were serologically positive and 8 had clinical signs of psittacosis (ornithosis). There were no deaths in this series, and the disease ran a comparatively mild course, with an atypical fever as the only clinical sign. Relapses were common, particularly after the discontinuation of chemotherapy (chlortetracycline usually gave good results). One patient, who worked with a flock of pigeons heavily infected with psittacosis, fell ill five times in six months with pneumonia before its cause was discovered. Another patient had a second attack of psittacosis eight months after his first. The serologic titer varied greatly, ranging in most cases from 1:120 to 1:240, but, in two patients with unquestionable acute psittacosis, the titer did not exceed 1:30 during several weeks' observation. In most cases epidemiological studies incriminated birds, particularly caged birds and pigeons, but there were some cases in which no bird contact could be found. Dr. P. M. Sörensen in *Ugeskrift for læger* for Sept. 1, 1955, discusses the possibilities of interhuman transmission of psittacosis. In his rural practice he has observed five patients, all living within a radius of 1 km. The first was a man, aged 43, whose influenza-like symptoms (severe cough, rhonchi, and purulent expectoration) led to serologic tests and the discovery of a psittacosis titer of 1:1,720. His infection could not be traced to any bird, and he was probably the infecting agent of two middle-aged women who simultaneously fell ill about three weeks after spending several hours with him at close quarters. Here, too, no bird contact could be found. One of these women was evidently responsible for serologically demonstrable psittacosis in her mother and son. Sörensen suggests that, when a febrile disease of the respiratory tract fails to respond to penicillin, psittacosis should be suspected even when there is no diseased bird to suspect.

The items in these letters are contributed by regular correspondents in the various foreign countries.

ENGLAND

Hypothermia for Postpartum Hemorrhage.—The use of hypothermia in the treatment of a patient with postpartum hemorrhage and apparently irreversible shock is described by Murray and Bruce in *Lancet* (**2**:699, 1955). A mobile obstetric team went to the home of a patient whose baby had been delivered by a general practitioner. As her systolic pressure was only 40 mm. Hg she was taken to the hospital, where, in spite of exploration, packing of the uterus, and blood transfusions containing norepinephrine, her condition slowly deteriorated. Within 12 hours she was moribund. Hysterectomy was considered to be the only way to stop the hemorrhage, other methods having failed, but, because the patient was unfit for operation under conventional anesthesia, it was decided to use hypothermia. A lytic cocktail containing 50 mg. of chlorpromazine, 50 mg. of promethazine, and 100 mg. of meperidine was injected intravenously in four equally divided doses. Cooling was also assisted by ice bags. Anesthesia was secured with thiopental, nitrous oxide, and oxygen. After operation of the patient rewarming was permitted spontaneously, and after a stormy postoperative period the patient recovered. It was considered that hypothermia, with its reduction in the oxygen requirement of the tissues, saved the life of this patient.

Milk-Borne Tuberculosis.—Dr. W. Lethem in the *Monthly Bulletin of the Ministry of Health Laboratory Service* (September, 1955, page 144) said that the case fatality rate for bovine tuberculosis in London had dropped from 136 in 1921 to 4 in 1953. This improvement is attributed to the fact that practically the whole of London's milk supply is now pasteurized or sterilized, whereas 30 years ago only about half was pasteurized. Deaths from this cause in children in rural districts also fell from 252 per million in 1921 to 12 in 1953. Nevertheless, untreated and untested milk is still being used in many rural districts. Last year many cases of tuberculous adenitis were reported in the Marlborough area, with 15 of these cases traced to one tuberculous cow. The proportion of milk produced from tubercle-free cows is now 58%. Tuberculosis has recently been cleared from four more areas in Great Britain: one in the northwest, one in mid-Wales, and two in Scotland. Since March, compulsory tuberculosis testing has been carried out in these areas and reactors have been slaughtered. About 80% of all herds are now in attested areas. According to the Ministry of Agriculture there are over 5,250,000 attested herds in Britain compared with 2,250,000 five years ago.

Allergy to Penicillin.—In the *British Medical Journal* of Aug. 20, B. J. O'Driscoll quotes the Minister of Health as saying, relative to allergy to penicillin, "The position with regard to desensitization is confused. Some dermatologists state roundly that it is useless." He then claims that a nurse can be desensitized to penicillin, although her desensitization may be somewhat more difficult than that of a patient. The Ministry of Health reports that many nurses have abandoned their career on account of sensitivity to penicillin. After describing a patient in whom the sensitivity was manifested by swelling of the eyelids when she worked in a room in which penicillin had been used, even though she did not handle it, the author outlines the day-to-day treatment until after the 27th day, when treatment ceased. The patient did not then react to 10,000 units intradermally, and a similar dose

a year later produced no effect. Antihistamines are much more effective when given intramuscularly, and if given this way, it is possible to effect desensitization in a fortnight.

Lord Nuffield's Gift.—At the annual dinner of the Royal College of Obstetricians and Gynecologists in September in London, the president of the college announced that Lord Nuffield had personally donated $210,000 to the fund that is being raised to build, equip, and maintain the new headquarters of the college. Another $140,000 is being given for the same purpose through the Nuffield Provincial Hospitals Trust. The new headquarters will be named Nuffield College, Regent's Park. Lord Nuffield, who was present at the dinner, said that it was time that obstetrics and gynecology were included in his benefactions and that he wanted to do everything he could to make childbirth safe.

Poliomyelitis Vaccine Tests.—Trials of British-made poliomyelitis vaccines will be made this winter. By then any danger of epidemics of the disease will have passed. The trials will be on a small scale, but they will involve the inoculation of volunteers or children whose parents have given written consent. Before this, stringent laboratory tests of the safety of the vaccines will be made, and their potential efficacy will be tried in animals. At least two modifications of the Salk vaccine will be tested. Before the trials can take place, tests of the blood of the recipients are necessary to determine what amount, if any, of naturally acquired immunity they possess.

Blood Transfusions.—Miss Hornsby-Smith, parliamentary secretary for the Ministry of Health, said at Sheffield that 70 times more blood was being used in hospitals than before the war. To meet this demand more than one donation was required for every minute, day and night, throughout the year. Transfusion has made possible surgical operations that in many cases would not have been attempted previously. A few minutes of a donor's time may mean a lifetime to someone else.

ITALY

Histoplasmosis.—At a scientific meeting in Reggio Emilia in February, Professor Bettolo said that histoplasmosis, once believed to be limited to the tropics, has become common also in temperate climates. It is characterized by pharyngeal and gastrointestinal ulcers, hepatosplenomegaly, and suppurative lymphadenopathy. The disease is often fatal, but there is a benign form that produces calcified areas in the lungs. Diagnostic examinations include the complement deviation test, the intradermal test with histoplasmin, and biopsy. Intracellular microorganisms are found in the lungs, liver, other organs, and the blood. In differential diagnosis all forms of enterocolitis accompanied with hepatosplenomegaly should be considered. In temperate climates the differential diagnosis should also consider tuberculosis of the lungs and bones, brucellosis, pulmonary neoplasm, and leishmaniasis.

Tissue Therapy with Human Placenta.—At a meeting of the "Filippo Pacini" Medical Academy in Pistoia in May, Professor Petragnani said that human placental extracts were first used in the treatment and prophylaxis of exanthematous diseases; that they favor the cicatrization of the lesions of lupus; and that they strengthen the general condition of children with ringworm. Placental extract therapy also has a marked therapeutic and prophylactic value in older persons. In none of the many adults who were treated with extracts or suspensions of placenta were cancers observed, despite the fact that in some of them cancer had been suspected. Whether this is significant or not is not yet clear.

Syphilis.—At the international convention on venereology in Catania in April, it was brought out that today the clinical aspects of syphilis have markedly changed and that the classical entities are becoming progressively rarer. This has led many specialists to assume that the disease is disappearing. On the other hand, the new diagnostic laboratory tests are revealing numerous asymptomatic forms that are serologically positive.

NETHERLANDS

World Congress of Anesthesiologists.—The World Congress of Anesthesiologists was held at The Hague in September. Dr. Woolmer of Bristol, England, said that patients with tetanus, bulbar poliomyelitis, or poisoning by barbiturates or central nervous system depressants should be placed prone in the head-down position and ventilation secured either by a cabinet respirator or by changes in airway pressure. Tracheostomy may be necessary if controlled respiration is given for any length of time; 40 to 50 liters of air a minute at a pressure of 12 to 14 cm. H_2O should be given. Either the pH of the blood or the arterial carbon dioxide tension should be measured to serve as a guide to adequate ventilation. Other useful determinations are the minute volume of respired air and the pH of the urine. Every two hours the patient should be turned. Dr. Bromage of Chichester, England, said that there is an increase in vital capacity with artificial lowering of the blood pressure, except in patients with cardiac or pulmonary disease who are already dyspneic. Dr. Pedersen of Hillerfol, Denmark, interpreted many of the changes occurring during anesthesia in terms of the general adaptation syndrome. Thus, the excitement stage in classical anesthesia corresponds to the alarm reaction. The catabolic phase of the syndrome occurs after a major operation, with negative nitrogen and potassium balance, and hyperreactive patients may die in exhaustion if the catabolic phase is prolonged, or go into shock if the alarm reaction is not terminated.

At the meeting on artificial hibernation and hypothermia, Dr. Gray of Liverpool, England, described experiments suggesting that the good effects of inducing hypothermia in a patient are due to conservation of the stress responses for the recovery period, instead of allowing these responses to exhaust the patient at the time of operation. With induced hypothermia, the excretion of cortical steroids remains more or less at the preoperative level. Dr. Lucas of London, England, said that it was possible to cool animals to 32 F (0 C) for short periods without any harm, and he wondered if this could be done in man, as at this temperature the oxygen requirements are negligible. Professor Virtue of Denver, Colo., described the technique that he used, which consisted of cooling a subject to about 86 F (30 C) with ice water, using a muscle relaxant to control shivering, and warming the subject after the operation by diathermy. The electrocardiogram is recorded continuously and a defibrillator kept at hand in case auricular fibrillation develops.

At the section on hypotension in anesthesia, Dr. Rollason of Hull, England, said he had studied the electrocardiograms of patients before, during, and after hypotensive techniques but found no permanent changes. At the time when the blood pressure was lowered, ventricular systoles often appeared and changes occurred in the S-T segment and T waves but these were transient. Dr. Hale of Cleveland, Ohio, said he secured a fall in blood pressure by using an intravenous drip of Arfonad and simultaneous withdrawal of blood. Thrombosis is a serious drawback to all hypotensive techniques. Hypotension should only be produced if it gives the patient a better chance for survival—not because it is more convenient for the surgeon. Dr. Kern of Paris, France, said he had not had a single death in 600 cases, but he considered that 20% of the cases were failures. He did not use controlled respiration routinely because it reduced the effective amount of blood in circulation and the cardiac return. On the other hand, Dr. Enderby of London, England, said he used assisted respiration, because hypotension with suboxygenation was dangerous. Gentle positive pressure in the anesthetic apparatus also permits additional control of blood pressure. This view was supported by Dr. Organe, also of London, who said he used posture, respiratory control, and vasodilatation to control blood pressure. Dr. Gillies of Edinburgh, Scotland, said that hypotension in operations was best secured by a spinal block with procaine. Myocardial and renal hypoxia occur if the blood pressure falls below 60 mm. Hg. Posturing the patient is important. His general mortality figure was 3.5%, which compares well with 2.6% for all controls.

Anesthesia, using the new steroid Viadril intraveneously, was described by Dr. Guardagri of Los Angeles, Calif. By using a

fast-running intravenous drip and a 2.5% solution, he overcomes the initial trouble of phlebothrombosis. Recovery is similar to that following therapy with thiopental, but Viadril appears to produce less respiratory depression than does thiopental. There is a synergism between the action of Viadril and opiates and anesthetic drugs, and when they are used smaller doses of muscle relaxants are needed. Some patients do not need a muscle relaxant if Viadril is given. Unlike thiopental, it is a true anesthetic agent. Dr. Guardagri has used it in cranial operations lasting nine hours.

Two new muscle relaxants were mentioned at the congress. Dr. Frey of Heidelberg, Germany, described the use of Prestonal in 1,000 patients. This acted within a minute or two, and the action lasted for five to seven minutes. The patient was mobile within half an hour. Although it acted rapidly like succinylcholine, pharmacologically it had a curare-like action. Another relaxant, Imbretil (hexamethylene-1,6-biscarbaminoylcholine bromide) was mentioned by Professor Brücke of Vienna, Austria. This had an initial action like succinylcholine, followed by a curare-like paralysis. Since its action lasts about 30 minutes, it might be of value in the treatment of tetanus.

NEW ZEALAND

Cancer.—Sir Stanford Cade and Prof. B. W. Windeyer of the British Empire Cancer Campaign visited the hospital centers in the main cities of Australia and New Zealand. In Dunedin in September, Sir Stanford Cade emphasized the fact that the patient suffering from cancer should be treated as a "unit," paying more attention to the person than to the mere removal of the pathological lesion. He opposed drastic amputations for advanced cancer of the stomach and produced convincing figures showing that longer survival has been obtained with partial removal and radiotherapy. The same principle applies to osteosarcoma of the leg in children. Professor Windeyer extolled the advantages and limitations of supervoltage radiotherapy units and the cobalt unit as compared with the conventional ones. His remarks were most timely, as the citizens of Dunedin have recently raised a fund to acquire a supervoltage unit for the Public Hospital.

New Zealanders Become Medicine "Addicts."—New Zealanders spent a record $8,500,000 in the last fiscal year appeasing their "increasingly unhealthy appetite for medicine," the annual report of the health department showed. The drug bill was $336,000 more than that for the previous year and three times the cost 10 years ago. Prescriptions dispensed under health benefit schemes now exceed 10,000,000 yearly. New Zealand has a population of 2,095,000.

PERU

Pyemia in Burned Children.—Dr. A. Bazan Altuna reports in *Review of the Children's Hospital* (vol. 17, no. 61, March, 1955) that since 1952 he has seen fatal pyemia caused by Pseudomonas aeruginosa in 35 of a series of 680 burned children. This complication usually developed between the third and fifth day after the accident and is related not to the extent of the burn but to the depth of it, since it occurred mainly in children with third degree burns. This infection in burned children appears in a fulminating and in an acute form. The fulminating form begins with the appearance of a green or blue-green secretion on the burned areas. Shortly thereafter, the burned surface becomes black and has the characteristic odor of P. aeruginosa infections; then, fever, dyspnea, abdominal distention, intense thirst, nervous irritability, delirium, headache, anorexia, and oliguria appear. After 24 to 36 hours the body temperature becomes subnormal and numerous and scattered, violaceous, subcutaneous nodules appear in areas of normal skin. Pearly vesicles appear at the center of these nodules and break, leaving a necrotic ulcer. The abdominal distension and dyspnea gradually increase, anuria succeeds the oliguria, and the blood pressure drops abruptly. Death occurs within 48 hours after the appearance of the nodules. Thirty-one of the children in this series had this form, and all died. In the acute form, which runs a less severe course, the nodules form and progress more slowly. If death occurs, it is several days after the appearance of the nodules. Dr. Bazan believes that pyemia in burned children passes through a prodromal phase in which only the local changes of the burned areas are detectable; a septicemic phase in which the systemic symptoms become prominent; and a third, or pyemic phase, which begins when the body temperature falls and the subcutaneous nodules appear. The blood culture was positive in all 35 cases. Smear cultures from the vesicles also revealed P. aeruginosa. Urine culture leads to the earliest diagnosis since it is positive in the prodromal phase, when there is still some hope of successful treatment. In this infection intense anemia and leukopenia with lymphocytopenia are the rule, despite the fact that every burned patient tends to show a leukocytosis. Although polymyxin is considered a specific for this type of infection, it has failed to cure it in burned children. Of the four children who had the acute form in this series, three in whom urine culture allowed an early diagnosis were saved by intensive treatment with a combination of polymyxin and tetracycline in large doses, started as soon as the diagnosis was made.

Insulin Coma.—Dr. Alfredo Saavedra's work on the psychopathological symptoms that arise on awakening from insulin coma has won him the Daniel A. Carrión award, annually given for the best Peruvian work in medical research. Dr. Saavedra analyzed the psychological data obtained from 19 psychotic patients who were interviewed as soon as they completely returned to consciousness after insulin coma. No person knew before undergoing insulin coma that he was going to be interviewed regarding his experiences on awakening. Some patients, when questioned, said that they had suffered many psychological symptoms, others only a few, but in no instance were symptoms entirely absent. No relationship between the psychological life of the patient prior to the onset of his psychosis and the type and pattern of the psychopathological symptoms on awakening was observed. These symptoms of alterations of consciousness in the order of their importance were: changes in perception, ideation, instinctive tendencies, affect, will, attention, consciousness of time, and memory. These symptoms were similar to those observed in patients poisoned with Opuntia cylindrica (a cactus) and *d*-lysergic acid diethylamide. They had no apparent relationship to the patient's psychosis. The delusions of five schizophrenic patients either persisted or increased in intensity during the awakening period in contrast to what happened to the other patients whose alterations of ideation were entirely unlike those they exhibited as components of their disease. The symptoms observed on awakening decreased in number and intensity as the patient recuperated and his mental condition improved. Of the 19 patients studied, 17 had schizophrenia, one syphilis with a depressive state, and one dipsomania with a hypophysial disorder.

Medical Insurance.—The chief executive of the Peruvian government has proposed a law requiring sociomedical insurance for employees. The Peruvian Medical Federation has gone on record as requesting that the law take into consideration the following conditions: 1. The insured must be free to choose his physician and his hospital. 2. The benefits of the insurance must be limited to the insured and not be transferable. 3. The insurance must cover all persons who are medically indigent. 4. The medical profession must be duly represented in all official committees having to do with the medical care of the insured. 5. The fees paid to physicians by the National Social Security Fund for professional services must be periodically readjusted. 6. Adequate medical services, including the development of preventive measures, must be organized. 7. The preventive and curative functions of the insurance should be coordinated with those of other governmental and private agencies. 8. The Social Insurance Agency must only foster the public health and avoid political, economic, or administrative influence. 9. The physicians should be appointed only on the basis of professional competitive examinations, and those who do not render efficient and adequate service must be dropped. 10. A minimum time for professional consultation and a maximum number of patients that

a physician working for the Social Insurance Agency may attend per hour and per day must be established. 11. The principle of privileged communication must be maintained.

Erythropoietic Effect of Plasma.—At a symposium on recent advances in medicine at the Sanitas Institute of Lima, Dr. César Merino and his co-workers of the Instituto de Biología Andina reported that the plasma of persons living at high altitudes stimulates erythropoiesis. The authors gave 15 healthy medical students an intravenous injection of 200 cc. of plasma from persons who lived 4,000 to 5,000 m. (12,960-16,200 ft.) above sea level. On the second day after the plasma was given, the reticulocyte level began to rise, reaching a peak on the third day, with a count of 1.5 to 1.65%. The levels returned to normal on the fifth and sixth days. Before the injection, reticulocyte count in the students was 0.4 to 0.8%. Later, the same students were given 200 cc. of plasma from persons living at sea level, with no change in their reticulocyte level. Likewise, plasma of patients with polycythemia vera injected into some of these students had no stimulating effect on the hematopoietic system.

Homage to Hipólito Unanue.—The Faculty of Medicine of the National University of San Marcos of Lima held ceremonies celebrating the second centenary of the birth of Hipólito Unanue, a Peruvian physician and teacher in the days when Peru was ruled by Spain. He founded the Anatomic Amphitheater in 1792 and in 1811 founded and was first president of the Royal College of Medicine of San Fernando of Lima, which during the first period of the republic became the Faculty of Medicine of the University. He is, therefore, regarded as the father of Peruvian medicine. He was also a leader in the movement for Peruvian independence and became Secretary of the Treasury and a member of the congress that drafted the first constitution of the Peruvian Republic in 1823. He later became president of the congress. He died in 1831.

Sterility.—El Hogar de la Madre, the Peruvian institution that gives medical assistance to expectant mothers and their babies, is installing a special department for the investigation and treatment of sterility in both men and women.

SPAIN

Medical Education in Spain.—Dr. J. García Orcoyen of the University of Madrid said that one of the most serious problems of medical schools is the plethora of applicants without proper qualifications. Two years ago, the Faculties of Medicine of Spain established a special course to facilitate the selection of students, prior to their enrollment in medical school. This has done much to reduce the number of applicants. The teaching of medicine should be strictly objective, and greater emphasis must be placed on the needs of the general practitioner rather than on preparation for a specialty. It is important to develop in the medical student the tradition of the physician who is the friend and confidant of his patients.

SWITZERLAND

Drugs That Act on the Brain.—Dr. B. B. Brodie of the National Heart Institute of the United States reported to the Vaud Medical Society in Lausanne on recently discovered drugs that act on the brain. Enteramine (5-hydroxytryptamine) was found by Italian workers in the argentaffin cells of the stomach. In the United States a chemically identical substance was isolated in the blood and was called serotonin. This substance constricts smooth muscles and has an antidiuretic effect, probably through vasoconstriction in the renal vessels. Serotonin is found in thrombocytes and is thought to play an important part in arresting hemorrhage by virtue of its vasoconstricting power. More recent studies have shown that it is also present in the brain, especially in the hypothalamic region. Another substance, LSD (*d*-lysergic acid diethylamide), was obtained from rye ergot. Workers doing research on this product became affected with severe psychic symptoms that disappeared after a few days of rest. The symptoms were at first attributed to depression resulting from overwork, but they reappeared after the workers resumed contact with the product, and it was found that an injection of from 50 to 100 mg. of *d*-lysergic acid diethylamide produces symptoms of schizophrenia that last 10 to 12 hours. In Scotland, it was discovered that only *d*-lysergic acid diethylamide can block the strong vasoconstriction of the coronary arteries and isolated uterine muscle caused by serotonin.

Reserpine, which has an indol nucleus, as do serotonin and *d*-lysergic acid diethylamide, has produced clinical cure in many schizophrenics who had been considered incurable. Chlorpromazine was originally designed for use as an antihistaminic but was unsatisfactory in that role. Later, its multiple and remarkable effects on hypertension, nausea, and vomiting were discovered. There is today no other product that has such a diversity of uses. Dr. Brodie studied the potentiating action of chlorpromazine on ethyl alcohol and the barbiturates in mice. The duration of sleep induced by these products is prolonged by the administration of chlorpromazine without the development of narcosis. When stimulated, the animal is easily awakened; then, he goes to sleep again. Serotonin has the same potentiating action. The administration of *d*-lysergic acid diethylamide blocks the potentiating action of either of the two agents. Reserpine administered to a dog produces the appearance in the urine of a large quantity of 5-hydroxyindolacetic acid, which is a disintegration product of serotonin. This suggests that reserpine acts by liberating serotonin in the body. Presumably it is the serotonin from the cells in which it is naturally found. The concentration of serotonin is especially high in the intestine, 10 mcg. per gram of duodenum in the rabbit. After administration of reserpine in a dose of 1 to 5 mg. per kilogram of body weight, serotonin disappears from the cells in which it has been stored. The nervous system is probably not influenced by the liberation of serotonin from the intestine, but by the serotonin contained in the brain. Until three years ago it was impossible to measure the concentration of serotonin in the brain by chemical methods. With the help of the zenon lamp fluoroscope, however, it is possible to verify the disappearance of serotonin from the cerebral tissue after reserpine administration. The drug does not take effect for two or three hours. The pathogenic role of serotonin has been demonstrated in certain types of tumors.

Clinical Trials with Prednisone.—A. F. Muller (*Schweiz med. Wchnschr.* **85:**1001, 1955) gave prednisone to 16 patients as initial treatment or after a course of cortisone therapy. The usual dose gives good results in arthritis and causes no water retention, but it may cause slight euphoria. In lupus erythematosus disseminatus, results of therapy with the drug were variable: amelioration of the clinical symptoms could be accomplished with doses of the drug four times less than those of cortisone needed to achieve this effect, but the drug maintained the signs of hypercorticalism induced by cortisone without, however, aggravating them. In one patient, the hydrosaline retention induced by cortisone corrected itself slowly under prednisone therapy, and in another the disappearance of edema was spectacular. Muller treated a patient with idiopathic sprue and lymphosarcoma in acute exacerbation after withdrawal of corticotropin. On the first day 50 mg. of prednisone was given. This dose was diminished by 5 mg. every day until a dose of 15 mg. was reached. This therapy caused cessation of diarrhea, paling of the dermatosis, decrease in edema, and improvement in the general status. On the ninth day, however, bronchopneumonia with hyperpyrexia developed. Penicillin therapy made the patient afebrile within two days, but then she began to show aggressiveness, agitation, and visual hallucinations. Two days later, she died after occurrence of massive melena without prodromal signs. Autopsy showed numerous fresh ulcerations of the small intestine. Gastrointestinal hemorrhages caused by prednisone have often been reported, but this appears to be the first case in which ulcerations in the small intestine occurred. Muller observed results comparable to those obtained with cortisone in the treatment of thrombocytopenic purpura, asthma, arthrosis, and plasma cell myeloma. The lack of water and salt retention makes prednisone more suitable for therapy in cardiac, hypertensive, and elderly patients.

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World Health Organization.—At the fifth regular session of the World Health Organization Regional Committee for Europe, held in Vienna in September, detailed plans for the following years were made and general guiding lines for World Health Organization policy in Europe during 1957 to 1960 were formulated. The principal aims will be to exchange experience in common health problems and to develop training facilities for medical and health personnel. The committee endorsed a training course on protection against radiation, to be held in November and December of this year. It is intended for physicists concerned with health problems and will be given in the Karolinska Hospital in Stockholm, Sweden. Subjects to be taught include laboratory design, the protection of factory workers, and the disposal of atomic wastes. After the resolution taken by the World Health Assembly that an attempt should be made to eradicate malaria all over the world, the committee agreed that close intergovernmental cooperation will be necessary if this goal is to be accomplished. Changes in health services necessitated by the aging of populations was informally discussed. In Sweden, with its almost 7 million inhabitants, about 10% of the population is above the official retiring age of 67 years, and this percentage is gradually increasing. In Great Britain, 75 to 80% of the general practitioners' house calls and 89% of those of the district nurse are for people over 65 years of age. The keynote of the discussion was that mere preservative care for older persons is no longer good enough. When ill, they should be treated with the same energy and skill as any other age group, and no effort should be spared to restore them to mobility and, as far as possible, to health. Admission to hospital is often a shock for an older person and because of this, as well as for financial reasons, older people should be treated at home if possible.

Prednisone Used in Rat.—Numerous researches undertaken to isolate a hormone analogous to but more active than cortisone led to the discovery of two synthetic steroids, prednisone and prednisolone. Since experiments performed in the rat have been few, Ducommun and his co-workers (*Schweiz. med. Wchnschr.* **85:**1000, 1955) studied the anti-inflammatory properties of prednisone in dextran-induced experimental arthritis in the normal rat and the glyconeogenic and lympholytic effects in the adrenalectomized rat. The anti-inflammatory action of prednisone is four or five times that of cortisone. The catabolic or antianabolic effect is equally strong. The glyconeogenic effect increases with the dosage. Comparable results were obtained with 500 mcg. of prednisone and 2.5 mg. of cortisone. Clinical results have shown that prednisone differs from cortisone in that it has no effect on the electrolytes. Prednisone maintains life in a rat that has undergone adrenalectomy and that is then subjected to stress, even though no sodium chloride be added to the drinking water. This effect is in direct proportion to the dose given. Like the glucocorticoids and unlike aldosterone, prednisone can be the cause of atrophy of the lymphoid organs (thymus, spleen, and lymph nodes).

Digestive Hemorrhage After Salicylate Therapy.—Gastric hemorrhages and perforations occur after cortisone or phenylbutazone therapy, but the occurrence of these accidents after the administration of salicylates is not well recognized. P. Secretan (*Praxis* **44:**837, 1955) reported the case of a man with a history of ulcer that had remained quiescent for seven years who unexpectedly had massive gastric hemorrhage after 12 days of salicylate therapy with a dose of 5 to 6 gm. per day. The author discusses the irritant effect of aspirin on the gastric mucosa and the cortisone-like mode of action of aspirin. The abruptness of the episode and especially the lack of premonitory epigastralgia speak against the local irritant effect of aspirin. If the conclusions of Roskam are correct and salicylates do act by stimulation of the adrenal cortex, directly or by way of the infundibulohypophysial system, then salicylates are very likely to cause accidents in the digestive tract identical to those that sometimes interfere with corticoid hormone therapy.

Treatment of Infantile Vomiting.—Vomiting is always a reflex action, whether it be caused by stimulation of the pharyngeal wall, irritation of the stomach or abdominal viscera, or by exaggerated excitability of the bulbar center. R. Martin Du-Pan (*Praxis* **44:**835, 1955) treated 200 infants and children afflicted with nausea or vomiting from various causes with drops, tablets, or suppositories containing 0.5 to 1 mg. of chlorpromazine per kilogram of weight. Results were usually good and sometimes spectacular in the medical cases; after surgical narcosis, however, only half the children were benefited. It is suggested that the dose might have been too small to inhibit the vomiting reflex in the unfavorable cases.

TURKEY

Thrombocytopenic Purpura.—In the *Bulletin of Istanbul University Medical Faculty* Tavat and his co-workers described a 21-year-old woman whose allergy to quinine caused her to have hemorrhages, destruction of the bone marrow, and thrombocytopenic purpura. Two years prior to admission, because of a cold, she had taken tablets containing quinine. Four hours later she had nausea and vomited. The next day her skin itched, and red patches appeared on her arms, legs, and chest. This rash lasted four days. Ten days prior to admission she had another cold with a temperature of 102.2 F (39 C). She was given 0.1 gm. of quinine and 0.15 gm. of acetophenetidin three times daily. On the third day pinhead to lentil-sized patches developed on her arms, legs, and chest. There was no effusion, but soon the patches became purple. No itching, fever, or allergic symptoms were noted. On the day before admission a severe gingivitis appeared. She was given calcium and vitamins C and K. On the morning of admission she vomited dark, clotted blood and her stools were black. On admission purpuric patches that did not disappear on pressure were present on her arms, legs, and chest. Her gums were bleeding. Blood pressure was 95/70 mm. Hg. The erythrocyte count was 2,840,000 per cubic millimeter, with 55% hemoglobin; leukocyte count was 7,350 per cubic millimeter; and thrombocyte count was 79,000 per cubic millimeter. The bleeding time was 21.5 minutes; clotting began after 4 minutes and was complete in 11 minutes. Scanty clot retraction began after 10 hours and was complete in 48 hours. The prothrombin time was 16 seconds. The sedimentation rate was 88 after one hour. The stools contained blood. The myelogram revealed 40.4% polymorphonuclear neutrophils, 1.8% eosinophils, 0.2% basophils, 7.2% transitional cells, 5.8% metamyelocytes, 16% myelocytes, and 1% myeloblasts. The reticular cell count showed 0.4% plasmocytes, 1.4% lymphocytes, 0.2% macrophages, 17.3% normoblasts, 2% immature macroblasts, 3.4% mature macroblasts, 0.6% proerythroblasts, and 0.2% megakaryocytes. On the slide nine small megakaryocytes were seen. Their cytoplasm did not show homogeneous basophilic stripping, and they had no granules. Their nuclei had no lobuli, and they were not surrounded by thrombocytes. The gingivitis subsided after 24 hours. On the third hospital day there was a slight recurrence. The patient was given a minimal subcutaneous injection of 0.1% solution of quinine in her left arm. After 6 hours an edematous field, 4 cm. in diameter, developed, and after 24 hours the center of this area was necrotic. There was no change other than a little redness for two hours at the site of the control injection on the right arm. After 20 days in the hospital the thrombocyte count was 278,000 per cubic millimeter; the bleeding, coagulation, and clot retraction time were normal, and the patient was discharged.

Chyliform Pleurisy.—In *Bulletin of Istanbul University Medical Faculty* (vol. 14, no. 2) Soysal and Umur reported a case of chyliform pleurisy in a 7-year-old boy who for three months prior had a distended abdomen. There was no fever or abdominal pain. The abdominal distention had progressively increased, and edema had developed in his legs. On admission he had pitting edema of the face, lumbar region, and both legs. There was diminished thoracic fremitus at the base of the left side of the lung, and there was dulness to percussion from its apex to its base. The respiratory sounds were diminished, and souffles were heard over the right side of the lung. The pulse rate was 120 per minute and respiratory rate 40. The spleen was soft and was palpable 4 cm. beneath the costal margin. The erythrocyte count was 3,200,000 per cubic millimeter, with 55% hemoglobin, and the leukocyte count was 10,600 per cubic

millimeter, with 68% neutrophils, 26% lymphocytes, and 6% eosinophils. The serum protein level was 4.9 gm. per 100 cc. The cadmium test was positive. A roentgenogram of the chest showed an upward directed diaphragm, an extensive hilus shadow, an enlarged cardiac air space, and a homogeneous opacity at the base of the left thoracic region. Puncture of the pleural cavity yielded 150 cc. of chylous fluid in which there were 80% lymphocytes, 20% polymorphonuclear leukocytes, and no acid-fast bacilli. Cultures of the fluid were sterile. There was a mild sedimentation, but no pellicle formed when the fluid was left standing. The reaction was alkaline, and the specific gravity was 1.010. The Rivalta reaction indicated that the fluid was an exudate rather than a transudate. In the first few days after admission the effusion tended to spread. Dyspnea, cyanosis, and edema increased, and there was retention of urine and tachycardia. Thoracentesis brought relief. The patient had 13 thoracenteses in three months. Four liters of chylous fluid was evacuated. With the exception of three days, the patient was afebrile during that period. He was given vitamins A, C, and D, calcium, streptomycin, and aminosalicylic acid. The chyliform fluid became serofibrinous and gradually disappeared, and the patient was discharged as improved.

Syncytioma Malignum.—In the *Bulletin of Istanbul University Medical Faculty* (vol. 14, no. 2) Erez and Arisan reported on seven patients with a syncytioma malignum. In three, uterine hemorrhage was caused by a hydatid mole; in three it followed delivery or spontaneous abortion; and one patient had a carcinoma of the vulva. The diagnosis was made from uterine scrapings or microscopic section after hysterectomy. Hysterectomy was performed on five patients and, in each of these, was followed by radiotherapy. In one patient laparotomy revealed an inoperable tumor, and the abdomen was closed. In four patients the Aschheim-Zondek and Friedman tests were made and were 4+. These cases illustrate the importance of currettage as a diagnostic as well as therapeutic measure. Although the biological urine tests are confirming adjuvants, the diagnosis is based on the histological examination of tissues or scrapings.

CORRESPONDENCE

INFORMATION REQUESTED ON ACUTE CORONARY THROMBOSIS

To the Editor:—Since the current illness of President Eisenhower has brought acute coronary thrombosis still more into the limelight than it has ever been before and since it is important to have more information on the prevalence of this disease in the United States today, it occurred to me that the medical profession might afford at least a partial answer. I am, therefore, requesting all physicians of this country to answer the following questions. Answers should be signed but names will be kept confidential. I realize that many doctors may not see this notice, but enough may answer to make the effort worthwhile. I also hope that physicians who do see the notice will advise others about it and try to get as many as possible to send in their answers. If you have encountered no cases during the month write nevertheless and please so state. Please answer part 1 anyway and part 2 also if you have time.

Part 1: Acute Coronary Thrombosis, Sept. 24 to Oct. 23.—How many patients with unquestionable acute coronary thrombosis in your practice began their illness during the month following the onset of the President's illness on Saturday morning early, Sept. 24, 1955 (therefore from Sept. 24 to Oct. 23 inclusive)? These should be considered your patients and listed as such even though seen or treated transiently by some other physician in the emergency, by a consultant later, or by the staff of some hospital in which the patient is being treated. To avoid duplication, if the physician answering this request is in one of these other three categories just mentioned I would like him to differentiate between the patients whom he has seen for others (which he should note also) and those who are strictly his own patients. In addition to the actual numbers, further data are requested: (1) total number of cases of unquestionable acute coronary thrombosis broken down into personal cases and patients of other doctors, both groups as treated in emergency, seen in consultation, and cared for in hospital; (2) sex and age; (3) occupations (list by number of cases in each occupation); (4) national origins; and (5) mortality date listing if death occurred in the first 24 hours, later in the first week, later in the second week, later in the third week, or later in the fourth week.

Part 2: Cases Prior to June 25.—How many of your own personal cases of unquestionable coronary thrombosis are alive in whom the acute attack antedated by three months the President's attack, that is, with onset before Saturday, June 25? Are you still caring for or seeing them at intervals, long or short? How many cases of other doctors do you see as a consultant (please list separately)? Please give (1) total number; (2) sex and age, and (3) occupations (list by number), including whether back at full-time or part-time work, invalided, or already retired before attack or retired on basis of age since. Your cooperation will be most helpful and greatly appreciated. Your answers may be mailed to the undersigned.

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SKIN TESTING FOR PENICILLIN SENSITIVITY

To the Editor:—In the article "Feasibility of Skin Testing for Penicillin Sensitivity" published in THE JOURNAL, Sept. 17, 1955, page 191, Berger and Eisen present interesting data but unfortunately come to the wrong conclusion. They state that skin testing for penicillin sensitivity is unreliable and should be discarded, yet their patient in case 1 promptly developed anaphylactic shock after a skin test with 20 units of procaine penicillin. If such a penicillin-sensitive patient had not been tested but given a therapeutic dose of penicillin, which would be at least 15,000 times greater than the test dose used, a fatal reaction would most likely have resulted. This case alone is a concrete example of the value of skin testing for penicillin sensitivity. A careful history of previous sensitivity to penicillin is not the panacea for preventing reactions, as the authors indicate. Many patients have developed shock reactions as their first manifestation of penicillin allergy, and some reactions have proved fatal. The evidence is clear that skin testing for penicillin sensitivity not only is feasible but is occasionally a life-saving procedure. It will almost invariably detect the patient with reagins to penicillin who will develop a severe, immediate allergic shock or anaphylactic reaction following the administration of the antibiotic.

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TREATMENT FOR CEREBRAL THROMBOSIS

To the Editor:—It might prove useful to others for me to report briefly dramatic results in the recent treatment of a case of senile chorea with large doses of Reserpine. Having read the report of excellent results with this medication in Hutchinson's chorea by Lazarte and others (*Proc. Staff Meet. Mayo Clinic* **30**:358 [Aug. 10] 1955), I felt justified in using it in a patient who recently had had a cerebral thrombosis involving the arterial supply to the basal ganglia. Her chorea was so severe that she could not feed herself and she had to be supported by two people to walk across the room. After a few days of treatment with a total daily dose of 14 mg. of Reserpine, the patient walked normally and had practically no involuntary movements. The dose has been reduced slowly to 8 mg. a day, and the patient has maintained her improvement. She had had her disability for about two months, and it was felt that this improvement was not merely coincidental with administration of Reserpine.

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LAW DEPARTMENT

MEDICOLEGAL ABSTRACTS

Malpractice: Necessity for Expert Testimony.—The plaintiff sued the defendant, a psychiatrist, for damages for malpractice and malicious persecution. Judgment was for the defendant, and the plaintiff appealed to the court of civil appeals of Texas. Until June 6, 1951, the defendant had never heard of the plaintiff. On that day a minister contacted the defendant and arranged for the defendant to see him and the plaintiff's wife on the following day. The following day the wife related that about four months before she had told her husband that she had committed adultery; that he had made her go with him to confront the man; that her husband had then shot the man in the hand; that since then he had accused her of other affairs, including an affair with her father-in-law; that he made her say that two of their children were not his; that he accused her of being a nymphomaniac and a pervert; that he had threatened to shoot her; that he had locked her in the bathroom and threatened to cut her throat; and that he had physically beaten her on several occasions. Finally, the wife related that she had taken steps to obtain a divorce. After the consultation, the defendant physician gave the wife a written diagnosis or statement to the effect that her husband was suffering from paranoid schizophrenia, that he was extremely dangerous to his wife, that he did not know right from wrong, and that he should be committed to an institution. The defendant never personally examined the plaintiff. The defendant testified that from what the wife told him, he could see that the plaintiff's mental furies were becoming more and more frequent, in an ever-tightening spiral; that an explosion was about due; and that he, the defendant, thought the plaintiff could only get better if removed at once from where he could see or come into contact with his wife. The defendant additionally testified that he expected at the time of the consultation that the plaintiff, in obedience to suspicions that are symptomatic of the plaintiff's mental illness, would shortly put in an appearance and that twice that afternoon the plaintiff did call at the defendant's office. As a result of the defendant's diagnosis, the plaintiff was charged with mental illness and was confined prior to his trial. The evidence adduced by the plaintiff on the issue of negligence was a statement by a psychiatrist, who was called as a witness, that under the same facts he did not think he would have concluded that the plaintiff was a paranoid schizophrenic.

The court of civil appeals, following the rule that the negligence of a doctor in making a diagnosis must be proved by the testimony of a doctor in the same field of practice, held that the statement of the plaintiff's witness was insufficient to establish negligence. The witness merely stated that he would not have reached the same conclusion that the defendant reached; he did not testify that the defendant was negligent in making his diagnosis. The court held that proof of negligence to sustain an action for malicious persecution was the same as in a malpractice action. If there was no wrong diagnosis there was no lack of probable cause. Since there was no proof of wrongful diagnosis, the court affirmed judgment for the defendant psychiatrist. *Daniels v. Finney, 262 S. W. (2d) 431 (Texas, 1953).*

Malpractice: Burns After Removal of Wart by Roentgen Therapy.—The plaintiff sued for damages for injuries to his left heel allegedly caused by the negligence of the defendant physician. From a judgment for the defendant, the plaintiff appealed to the Supreme Court of North Carolina. On Dec. 3, 1947, and on Jan. 7 and 14, 1948, the defendant gave the plaintiff, a boy of nine years of age, x-ray treatments for a wart on his left heel. The rays were filtered through an aluminum sheet and focused on the wart by a cone, the tip of which was placed about one-half inch above the wart. The skin area around the wart was protected by a lead shield. After the first treatment the area around the wart became pink-red and tender. About eight days after the last treatment the wart fell off, and the spot where it had been eventually healed. The surrounding area remained reddish and tender, however, and the plaintiff saw the defendant several times during March, 1948. Thereafter he did not see him until January, 1950, but during the intervening period the heel remained inflamed and irritated, resulting in an ulcer. At the time of the 1950 visit, the defendant lanced the plaintiff's heel and gave him penicillin. Subsequently the plaintiff underwent two operations, the second involving a skin graft, which were performed by other doctors. The instant suit was filed on the theory that the plaintiff's condition was caused by excessive irradiation administered by the defendant physician. At the trial there was considerable testimony by medical experts, some of which supported the position that the ulcerous condition on the plaintiff's heel could have been caused by the x-ray treatments. Other portions of the testimony indicated that people vary, according to their particular skin tissue structure, in their reactions to x-ray treatment. There is no feasible way to determine what x-ray strength a person may safely stand, but there is a maximum strength generally accepted as the limit for most people's skin. There was no evidence that the defendant had either improperly operated the machine or administered x-rays beyond the strengths generally accepted as safe.

The Supreme Court held that the evidence presented no question of negligence on the defendant's part. The Court pointed out that a physician who possesses the requisite skill and knowledge and exercises ordinary and reasonable skill in administering an x-ray treatment is not liable for burns resulting from such treatment. The *res ipsa loquitur* doctrine, said the Court, does not apply merely because the machine was under the exclusive control of the defendant. The doctrine is applied only where the injury involved would normally not result from what took place unless the person in control of the situation acted negligently. Evidence failed to show that this was true. In fact, it showed that the injury involved could happen regardless of the care exercised by the operator of the machine. The Court therefore affirmed the judgment for the defendant physician. *Nance v. Hitch, 76 S. E. 2d 461 (N. C., 1953).*

Malpractice: Surgeon's Reliance on Diagnosis of Referring Physician; Statute of Limitations.—The plaintiff filed suit against a physician and surgeon for injuries from the performance of a vasectomy by the defendant surgeon. At the conclusion of the evidence, the trial court directed a verdict against both the defendants, who then appealed to the Supreme Court of Colorado.

The plaintiff testified that prior to the operation he had entered into a definite contract with the defendant physician to have a circumcision performed on him and that he had agreed to let the defendant surgeon perform the operation. The physician's testimony on the other hand was considerably different. It indicated that the plaintiff, through his wife, gave his consent to have a "tube-tying" operation performed and that a vasectomy was in fact expertly performed. The defendant surgeon testified that he was briefed before the operation as to what was to be done, that the physician told him that he had obtained the written consent of both the plaintiff and his wife for a vasectomy (which he learned later was not true), and that he had then gone ahead with the operation. The defendants contended that the plaintiff's action was one of assault and battery and therefore subject to the one year statute of limitations. The plaintiff, on the other hand, contended that the action was for malpractice and therefore subject to the two year statute of limitations.

The Supreme Court admitted that where a surgeon performs an operation to which the patient has not consented, an unlawful battery is committed, but the Court went on to point out that such a situation also amounts to malpractice. The failure of a physician to perform the operation to which the patient has consented can be viewed as negligence in the performance of the duty owed to the patient. A suit brought on this basis, therefore, is for malpractice founded on negligence and is not barred by the statute of limitations governing batteries. The Court held, however, that there was sufficient conflict in the evidence as to just what operation the parties did intend, to warrant submission of that issue to the jury. A verdict should not have been directed for the plaintiff. The Court also found that there was no malpractice on the part of the defendant surgeon, who was entitled to rely on the physician's diagnosis and on the physician's statement that he had obtained the patient's consent. Accordingly, the Supreme Court reversed both judgments, ordering that the suit be dismissed against the surgeon and that there be a retrial of the suit against the physician. *Maercklein v. Smith, 266 P. (2d) 1095 (Colo., 1954).*

MISCELLANY

HEAL THYSELF

Richard Gordon

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The public always appear surprised that doctors should fall ill, as though hearing that a policeman's house had been burgled or the fire station had gone up in flames. Doctors go sick fairly often, though they suffer differently from anyone else: they have only one disease, which presents both a *mitis* and a *gravis* form.

The *mitis* phase is characterized clinically by the usual symptoms of malaise, headache, shivering, loss of appetite, coughing, and insomnia. It usually lasts several days, while the doctor does his surgery sitting in an overcoat and wonders why he's becoming so bad-tempered. He shakes off his symptoms like a wet dog and makes a diagnosis of draughts, late nights, or over-work.

When he wakes up one morning with black shapes in front of his eyes he sneaks down to the surgery in his dressing-gown and stealthily takes his temperature. A hundred and four! This immediately ushers in the *gravis* stage of the illness. He snatches a textbook from the shelf and nervously flicks over the pages. The first disease he spots is typhoid fever. *Prostration . . . headache . . . cough . . . backache . . .* he reads, running his finger quickly along the symptomatology. He realizes nervously he has every one of these afflictions, locks the door, and tries to feel his own spleen.

Admitting he is a desperately ill man he staggers to bed, bringing with him every medical and surgical textbook he can lay hands on. Once comfortable on the pillows he can see the problems of diagnosis more clearly. There are several more alarming diseases than typhoid to attract him, and after a while he becomes certain he is in the grip of either cholera, smallpox, or plague. He takes his pulse, inspects his tongue in his wife's hand-mirror, and carries out a careful search of his entire body-surface for spots. Finally he settles for malignant endocarditis, a diagnosis that in his finals would have had him thrown out of the examination room.

He next faces the problem of treatment. Doctors' houses are well supplied with drugs by the manufacturing chemists, who supplement their advertisements in the morning mail with transparently-wrapped packets of samples. These are always stuffed into the bathroom cabinet where old tooth-paste tubes, rusty razor blades, and worn fragments of soap accumulate. Dragging himself out of bed, he finds a bottle of bright green pills and wonders what they are. He swallows a few and rummages about until he comes across some aspirins. Several more coloured packets then attract him, and he starts mixing himself a therapeutic *hors d'œuvre*.

Doctors require different doses from the general public. The patient who goes away with a prescription marked sternly ONE TEASPOONFUL IN AN EGG-CUPFUL OF WATER EVERY FOUR HOURS is frightened enough to assemble spoon, egg-cup, and kitchen clock and takes the dose as precisely as starting a race. But in the profession pills are generally taken in doses of ONE HANDFUL NOW AND THEN (or if they are particularly small ones, ABOUT A DOZEN), medicine administered as A LARGE SWIG PRETTY FREQUENTLY, and ointments and embrocations assumedly labelled RUB ON VIGOROUSLY UNTIL ALARMED BY THE CONDITION OF THE SKIN.

The doctor's wife, who has recognized for some days that he is suffering from 'flu, suggests she summon one of his colleagues. But doctors, like animals, prefer to be ill alone. He refuses to see anyone; and when she insists on telephoning a rival practitioner the consultation is usually embarrassing and unhelpful:

"Why, hello, Bill! Laid up, eh? Been taking your own prescriptions, ha ha!"

"Hello, George! Decent of you to come. Needn't bother about the old bedside manner in the trade, eh, ha ha!"

"What's the matter with you, Bill?" asks the visiting doctor.

"Well, I think I've got polyarteritis nodosa, or possibly methemoglobinæmia."

"Go on!"

"Yes. What symptoms should I have?"

"Oh, sort of pains in the limbs and so on."

"That's it exactly!"

"Well, I hope you get better."

"Yes, so do I. So kind of you to come along professionally like this. Good-bye."

Doctors recover in a different way from ordinary people. A layman is told to stay in bed for an extra week, and take a fortnight at the seaside; but a doctor, after taking his temperature every half-hour for a day or so, suddenly discovers he is completely cured. He at once gets up and puts on his clothes, and either goes downstairs and takes the evening surgery or makes for the garden to catch up with his digging. As most doctors will admit, they can't afford to be ill: they're not registered as patients under the National Health Service.

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MEDICAL FILM REVIEWS

Hard Brought Up: 16 mm., black and white, sound, showing time 41 minutes. Sponsored by the Mississippi State Department of Welfare with the cooperation of the Children's Bureau of the U. S. Department of Health, Education, and Welfare. Produced in 1954 by Nicholas C. Read, Potomac Film Producers, Inc., Washington, D. C. Procurable on purchase from Mental Health Materials Center, 1790 Broadway, New York 19.

This film makes some positive contributions to the understanding of the problem of juvenile delinquency, its genesis, and treatment. It stresses the importance of early recognition of maladjustment as a means of prevention. By drawing upon contrasting home situations, the film shows that the problem is not confined to slum areas, but may develop in a family that, to all appearances, offers favorable circumstances for normal growth and development. In the community portrayed, the judge of the juvenile court and the child welfare worker form a sympathetic team that provides professional help to children who get into trouble and to their families. The fact that the cast is drawn from the citizenry of Jackson, Miss., may be a drawback to its usefulness in all sections of the country, in that the accent and some of the cultural aspects are unfamiliar elsewhere. Second, the multiplicity of problems handled by the child welfare worker, each of which involves special skills, could well have been made the subject of several short presentations that would allow for an adequate discussion period. This film would lend itself to preprofessional student groups in medicine, law, psychology, social work, and the ministry. Church, civic, and parent groups would be appropriate audiences, as would educators and others who work with children. The film is well organized. The narration and photography are excellent.

Orbital Mucoceles: 16 mm., color, silent, showing time 22 minutes at sound speed. Prepared by Hans Von Leden, M.D., Northwestern University Medical School, Chicago, under the sponsorship of the William E. and Harriet B. Gould Foundation. Produced in 1955 by Mervin LaRue, Inc., Chicago. Procurable on rental ($5) or purchase ($165) from Hans Von Leden, M.D., 30 N. Michigan Ave., Chicago.

The purpose of this film is to describe the etiology of orbital mucoceles, to teach their diagnosis and differentiation from other orbital tumors, and to demonstrate the author's technique of their surgical removal. The diagnosis of an orbital mucocele is based upon a thorough ear, nose, and throat examination, complete eye studies, and roentgenograms. The differential diagnosis includes all neoplasms of the orbit. Three operative sequences are shown, two of which demonstrate removal of mucoceles and one showing the removal of a benign tumor. In the case of the mucoceles, the film shows the exenteration of the sinus and reconstruction of the nasal frontals using a tantalum funnel. The planning of the film is adequate; however, there is a paucity of titles. Two of the three operations could be advantageously omitted, thus shortening the film and rendering it more effective. This film will be of value to ear, nose, and throat and plastic surgeons.

The Termination of the Bile Duct: 16 mm., color, sound, showing time 16 minutes. Prepared by Julian A. Sterling, M.D., University of Pennsylvania, Philadelphia. Produced in 1955 by Davis & Geck, Inc., and Al Kane Productions, Inc. Procurable on loan ($3) or purchase ($100) from Al Kane Productions, Inc., 1411 Walnut St., Philadelphia.

This film is an anatomical study to demonstrate normal findings in untraumatized specimens of the termination of the bile duct. Photography, through methyl salicylate solution, depicts the termination of the bile duct and indicates the relationship of the course of the duct, the papillary sphincter, and the "common channel." The characteristics of the duct termination in choledocholithiasis and in pancreatitis are also visualized. It is indicated that the termination for the bile duct is not as an ampulla (normal in 5%) but a papilla. It is observed that the bile duct terminates through a papilla as described by Oddi, Dardinski, Boyden, and others. Forty per cent of specimens were found to have separate orifices for bile and pancreatic ducts. The other 60% were evaluated further with regard to the significance of the common channel. When an ampulla was present as the common channel within the papilla, 5% interductal reflux was possible. In most other cases it is demonstrated that the presence of a common channel does not signify the existence of interductal reflux. The author has used colored drawings and partly cleared specimens to demonstrate the anatomical points. Some of the drawings are not very skillfully done and detract somewhat from the appearance of the film. The ducts, as illustrated in the drawings, are quite small, perhaps corresponding to the small size of the duct in fixed specimens. This film is primarily of interest to surgeons interested in the biliary tract and could also be used for students of anatomy.

Industrial Dermatitis: 16 mm., black and white, sound, showing time 29 minutes. Produced by the Film Producers Guild with the cooperation of the St. Johns Hospital for Diseases of the Skin and Middlesex Hospital, London. Procurable on loan from Imperial Chemical Industries (New York) Ltd., Film Library, 488 Madison Ave., New York 22.

This film begins with a sequence in which a young woman with a dermatitis on the hands visits a consultant. In the course of diagnosis of her case, some basic principles of dermatology including patch-testing are shown. Three years later, the woman is shown as a medical student in a school where the consultant is giving a lecture on dermatology. He first projects a film showing by animated diagram, the anatomy, physiology, and special susceptibilities and characteristics of the skin, and then another that contrasts various specifically industrial or occupational dermatoses with other similar types to stress the differential diagnosis. The presentation of the anatomy of the skin is excellent, as is the body of the picture showing real industrial dermatoses in connection with the industries in which they may be acquired. However, in several instances, diagnoses are used referring to occupational yeast and fungous infections. These concepts are at present refuted and completely outdated. If the long introductory sequence were completely cut and replaced with a shorter more pertinent introduction, and the erroneous diagnoses of different skin diseases were corrected, this film would be a worthwhile presentation to junior medical students. In its present form, it is not recommended.

Technic for Splenectomy: 16 mm., color, sound, showing time 24 minutes. Prepared by John L. Madden, M.D., St. Clare's Hospital, New York. Produced in 1955 by and procurable on rental or purchase from Sturgis Grant Productions, Inc., 322 E. 44th St., New York 17.

This film depicts clearly an accepted technique for splenectomy on a 53-year-old man with hypersplenism and selective erythrocytopenia and thrombocytopenia. A routine general exploration of intraperitoneal viscera revealed no gross abnormalities, but an accessory splenic nodule was found in the proximal portion of the gastrosplenic ligament. Mobilization of the greatly enlarged spleen is continued with division of the gastrocolic ligament and of a portion of the gastrosplenic; the accessory splenic nodule is removed. The spleen is further mobilized, the lienorenal ligament is divided, and the vasa brevia are clamped and cut. With division of the splenic artery and vein, the specimen is removed. The author is to be complimented for emphasizing the importance of proper immobilization before the actual removal of the organ is undertaken. The animated diagram that reviews the horizontal disposition of the peritoneum, illustrating a cross section of the abdominal cavity seen from below, adds appreciably in the orientation, particularly as it pertains to the ligamentous attachments of the spleen. Tissues are handled gently and hemostasis is adequate. A minor criticism that in no way detracts from the film is the usage of blunt dissection in lysis of the left leaf of the lienorenal ligament. It would have added much had exposure of this structure been possible and sharp dissection utilized in this particular step. This picture can be recommended to surgeons interested in the technique of splenectomy.

NEW FILM ADDED TO A.M.A. MOTION PICTURE LIBRARY

Eat for Health: 16 mm., color, sound, showing time 11 minutes. Produced in 1954 by Encyclopaedia Britannica Films in collaboration with James R. Wilson, M.D., Secretary, Council on Foods and Nutrition, American Medical Association. Procurable on loan (service charge $2) from Committee on Motion Pictures and Medical Television, American Medical Association, 535 N. Dearborn St., Chicago 10.

This film introduces a new approach to teaching children to eat a well-balanced diet. Using the five fingers of the hand as an always available check-off device, the film identifies a food group with each finger: bread and butter or margarine, milk and cheese, meat and eggs, vegetables, and fruits. This is the first film to present a food classification based on five rather than seven groups. Five groups lend themselves to finger-counting, which is an advantage with children who must be constantly reminded of the various food groups. In presenting the reasons for eating a balanced diet, the story shows a number of the leading child's schoolmates, who have profited from each of these particular foods. This film could be used most effectively at the junior high school level, although children in the intermediate grades would probably understand with the assistance of a teacher. It could also be used with adult groups to illustrate patterns for food selection and to provide a basis for aiding children with their eating problems.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

The Action of Glucagon on the Blood Sugar in Normal and Diabetic Persons. D. Hubble. Diabetes **4:**197-202 (May-June) 1955 [New York].

Purified glucagon was given by intravenous injection to 17 unselected diabetic patients of the ages between 21 and 74 years whose weights varied between 84 lb. (38.1 kg.) and 258 lb. (117 kg.). The blood sugar curves then were compared with those obtained by the Himsworth insulin-glucose tolerance test, the insulin tolerance test, and the glucose tolerance test. None of these patients had received insulin therapy, and all of them had been at rest in the hospital for three to five days on basal diets related to their surface area and with a carbohydrate content varying from 180 to 300 gm. (57.5% of total calories). Glucagon was also administered intravenously to three persons without metabolic disease in order to establish a normal response for this method. The response to intravenous glucagon also was determined in three diabetic children who had already been stabilized by insulin and in whom spontaneous variations of as much as 300 mg. per 100 cc. or more in a 24-hour period, as defined by Kirtley for his insulin-sensitive patients, had been observed. Glucagon raises the blood sugar both in healthy and in diabetic persons. The hyperglycemic response to glucagon in unstable, insulin-sensitive, young diabetics is small, but it may be equally low in diabetics of other types, whether assessed clinically or by the Himsworth test. The extent of the rise in blood sugar in diabetic patients is probably dependent on the amount of glycogen stored in the liver at the time of the test and can be enhanced by increasing the deposition of hepatic glycogen. The rate of subsidence of the hyperglycemia is an individual response, since it closely parallels the fall in the glucose tolerance curve. In three thyrotoxic diabetic patients, however, the fall was much faster after glucagon hyperglycemia than after alimentary hyperglycemia. In two diabetic patients and in three nondiabetic patients, the effect of glucagon and epinephrine, at first separately and then together, was investigated by blood sugar response. Results showed that the hyperglycemic response to epinephrine and glucagon injected simultaneously is greater than when either is injected alone, but the peak response is delayed by at least half an hour.

Syndrome of Idiopathic Hyperlipemia, Mild Diabetes Mellitus, and Severe Vascular Damage. D. Adlersberg and C.-I. Wang. Diabetes **4:**210-218 (May-June) 1955 [New York].

The syndrome of idiopathic hyperlipemia, mild diabetes mellitus, and severe vascular damage was observed in three men and two women. One woman had a normal body weight, while the other four patients were moderately to severely obese. The duration of the syndrome varied from four to seven years. Four patients, two of whom had mild hypertension, showed evidence of coronary artery disease and myocardial infarction; the fifth had thrombosis of the central retinal vein and loss of vision in one eye. Extensive hyperlipemia was noted in all five patients and was characterized by persistent milky serum. There was marked elevation of both neutral fat and total lipids, with elevated levels of free and esterified cholesterol and phospholipids. Restriction of calories and of dietary fat, combined in two patients with the use of insulin, resulted in a decided gradual reduction of serum neutral fat and total lipids as well as the other serum lipid fractions. One patient had severe acute pancreatitis with eruptive xanthoma. Two other patients had eruptive xanthoma that subsided with improved control of diabetes and lowering of serum lipids. The clinical manifestations and the abnormalities of lipid metabolism in the authors' patients with idiopathic hyperlipemia were compared with those in two women aged 43 and 48 years, respectively, who had hypercholesteremia of the xanthoma tendinosum type associated with diabetes mellitus. Hypercholesteremic xanthomatosis differs from idiopathic hyperlipemia in the clear appearance of the serum and in absent or only moderately elevated serum neutral fats. While only one of the patients with idiopathic hyperlipemia had a small pinpoint-sized lid xanthelasma, both patients with hypercholesteremic xanthomatosis had extensive lid xanthelasmas. In contrast to the three patients with eruptive xanthoma in the group with idiopathic hyperlipemia, neither one of the two patients with hypercholesteremic xanthomatosis had eruptive xanthoma. It is, therefore, advisable to separate idiopathic hyperlipemia associated with diabetes mellitus from xanthomatosis associated with diabetes mellitus on both clinical and chemical grounds. Although the alteration of serum lipids observed in idiopathic hyperlipemia with diabetes mellitus represents extreme changes of lipid metabolism, similar abnormalities of a lesser degree are probably present in other diabetic patients.

Abscess of the Pituitary Gland in a Diabetic Patient: The Houssay Phenomenon in Man. J. H. Brenner. Diabetes **4:**223-226 (May-June) 1955 [New York].

A 62-year-old woman who had had diabetes mellitus for seven years was admitted to the department of internal medicine of the Jewish Hospital, Cincinnati, suffering from septicemia. She died on the eighth hospital day. At first she required a small amount of insulin, but during the last few days of life she showed the Houssay phenomenon, in that she had a tendency to spontaneous hypoglycemia. Autopsy revealed virtually complete destruction of the pituitary gland by an abscess. There were widespread metastatic abscesses in the kidneys. A smear of the renal pus showed gram-negative bacilli, morphologically resembling Escherichia coli. The smear from a spinal tap that was made a few hours before the patient's death showed the same kind of bacilli; Esch. coli was probably the offending agent. Fever may have masked the metabolic response to destruction of the pituitary at an earlier date. The unusual observation of hypoglycemia after a relatively short fast in a patient whose fever has persisted can only be interpreted as caused by a severe destruction of the anterior pituitary gland with inadequate function of the cellular remnants. Death was probably caused directly by prolonged hypoglycemia.

Hepatic Coma: A Clinical and Pathologic Study. W. T. Foulk, H. R. Butt, M. H. Stauffer and others. Gastroenterology **29:** 171-183 (Aug.) 1955 [Baltimore].

This report is based on the records of 52 consecutive patients who were seen in hepatic coma at the Mayo Clinic. The diagnosis was cirrhosis in 23 of these patients, one of whom also had hemochromatosis. Nine patients had hepatitis; 4 had biliary cirrhosis secondary to common-duct stricture or stone; 11 had obstructive jaundice; and 5 had neoplastic malignant involvement or abscess of the liver. Ten of the 23 patients with cirrhosis had histories of an excessive intake of alcohol for years, 4 drank moderately, and 9 not at all. Of the remaining 29 patients, only one had drunk to excess. Spider angiomas were noted in only 12 of the 52 patients. Fetor hepaticus was noted in 24 patients. Many of the patients had had previous jaundice, and nearly all were icteric at the time of coma. Hepatic coma is seen most frequently in patients with primary parenchymal hepatic dis-

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ease, but it occurs as well in patients with obstructive jaundice or neoplastic disease of the liver. Although jaundice is commonly observed during hepatic coma, it is not a necessary accompaniment of this state. Impending hepatic coma must be suspected in any patient who has hepatic disease and who shows aberrations of consciousness. The onset may be insidious or rapid; often the disturbance first appears as confusion, restlessness or even wild agitation, during which the patient may become disoriented and dysarthric and may perform inappropriate acts or give evidence of paranoid ideas. Drowsiness supervenes and progresses to stupor and coma. With disturbances of consciousness, reflex changes and other neurological disturbances develop. No close correlation was noted between the clinical or laboratory evidence of severe hepatic dysfunction and the development of coma. Hemorrhage, infection, paracentesis, and surgical procedures appeared to be responsible for the onset of coma in some. Autopsy was done in 44 of the 47 cases in which death occurred. Pathological evidence of recent parenchymal damage was striking in 14 of the 20 cases in which the diagnosis at autopsy was cirrhosis; such evidence was present in all cases in which death was the result of fulminating hepatitis, obstruction of the biliary tract, or hepatic neoplasm. The mean weight of the liver was smallest in those in which fulminating hepatitis was the cause of hepatic insufficiency. The largest livers were found in patients in whom obstruction of the biliary tract or metastatic neoplasm accounted for the hepatic coma. Close observation of minor alterations is necessary to avert progressive deterioration. Early correction of abnormalities of fluid and electrolytic balance are likely to be ignored if the prognosis is viewed pessimistically. Fluid must be administered intravenously, while at the same time the physician must guard against overhydration. Recent studies relating to the role of ammonia in the genesis of hepatic coma suggest that the intake of protein should be reduced to a level of 60 gm. daily in patients with hepatic disease who manifest neurological abnormalities or disturbed consciousness. Controlled studies of various therapeutic programs on a scale sufficient to be conclusive are difficult to carry out in a situation so critical as hepatic coma. When a patient recovers, it usually is impossible to know what factors were responsible for the favorable outcome.

Chlorpromazine (Thorazine) Hepatitis. G. McHardy, R. McHardy and S. Canale. Gastroenterology **29:**184-188 (Aug.) 1955 [Baltimore].

An obstructive type of juandice, painless, associated with the characteristic liver profile and with histopathological findings of cholestasis in the biliary canaliculi, was observed following administration of chlorpromazine. A 59-year-old woman was given 40 mg. of chlorpromazine daily because of intense anxiety. Thirteen days later she had improved symptomatically but mild aphthous stomatitis had developed; the dosage was reduced to 20 mg. daily. Several days later, new symptoms, including headache, nasal congestion, vertigo, and nausea, led the otolaryngologist to suggest allergic rhinitis. The peripheral blood showed 7% eosinophils. Jaundice was obvious five days later. A tentative diagnosis of obstructive jaundice, presumably calculous in origin, was made, and the possibility of an obstructing neoplasm was considered. Jaundice became more intense, stools were acholic, and purpuric areas developed over the body. On exploratory laparotomy the gallbladder and common bile duct appeared normal. Nodes in the vicinity of the common duct appeared hyperplastic; frozen section histological examination confirmed benign hyperplasia. Operative cholangiography revealed normal common duct, hepatic ducts, and biliary radicles. Abnormal bleeding of the wound occurred postoperatively. The patient's convalescence was slow. Differentiation between chlorpromazine-induced jaundice and surgical jaundice is not positive unless resolution occurs promptly after discontinuance of the drug. The wound-bleeding tendency recorded in chlorpromazine-jaundiced patients is not explainable on the basis of hypoprothrombinemia, coagulation defect, abnormal bleeding time, or capillary fragility. The patient had an allergic tendency, suggesting hypersensitivity. The diagnosis of chlorpromazine hepatitis should be suspected when the symptoms and signs of obstructive jaundice occur during the first four weeks of chlorpromazine therapy. Apparently, it cannot be conclusively differentiated from extrahepatic obstructive jaundice by any presently available diagnostic methods. An allergic history and presence of eosinophilia may further incriminate chlorpromazine as the etiological factor.

Multiarticular Injections of Hydrocortisone in Treatment of Chronic Progressive Polyarthritis. R. Weismann-Netter, B. Krewer and P. Lorch. Presse méd. **63:**1153-1155 (Sept. 3) 1955 (In French) [Paris, France].

In 1954, the authors reported on their first six patients with chronic progressive polyarthritis treated by multiple intra-articular injections of hydrocortisone. These initial results were excellent, and experience with 30 additional patients has reaffirmed the value of this radical method. The injections cause no harm but usually provide immediate or slightly delayed relief to the patient, and therefore should be used liberally. They constitute the treatment of choice unaccompanied by other measures, especially in the moderately severe forms of the disease where there are irremediable deformities, but pain and disability can be influenced in such a way as to obtain recoveries that were previously unheard of. The therapy is in no way curative, but it has the advantage that a new course can be undertaken at any time with no fear of sensitization or resistance. The length of the period of sedation afforded by an injection varies from 2 to 12 months. The most valuable adjunct to the treatment is physiotherapy. The period of hospitalization is considerably reduced through the use of this method, and patients are able to resume limited occupations. Those who remain virtual invalids should be cared for in special homes.

A Comparative Study of Portal and Bilharzial Cirrhosis. H. F. Rodriguez, M. R. Garcia-Palmieri, J. V. Rivera and R. Rodriguez-Molina. Gastroenterology **29:**235-246 (Aug.) 1955 [Baltimore].

In an attempt to evaluate the significance of Schistosoma mansoni in the pathogenesis of liver cirrhosis, a clinical analysis was made of all available cases of cirrhosis at the San Patricio Veterans' Administration Hospital, San Juan, Puerto Rico, during the period from November, 1946, to April, 1954. The 112 cases of cirrhosis of the liver that were analyzed included 69 of portal cirrhosis, 22 of bilharzic cirrhosis, 11 patients with concurrent Schistosoma mansoni infestation and alcoholism, 7 cases of posthepatic cirrhosis, two of biliary cirrhosis, and one of transfusion hemosiderosis. Bilharzic cirrhosis occurred in younger patients and portal hypertension and hypersplenism were more frequent. Anemia, when present, was due to bleeding esophageal varices or hypersplenism. Liver function tests revealed a high incidence of abnormality in Bromsulphalein dye retention and alterations in plasma protein constituents. The patients with portal cirrhosis showed a higher incidence of edema and ascites, also of jaundice and of signs and symptoms attributed to endocrine disturbances. Leukocytosis was also encountered more often in portal cirrhosis, suggesting a more extensive hepatic necrosis. Anemia was of three types in these patients: due to loss of blood, associated with hypersplenism, and of the macrocytic type. Bleeding esophageal varices and hepatic insufficiency were the immediate causes of death in the cases of portal cirrhosis, whereas bleeding varices and postoperative complications following an esophagogastrostomy were the main causes of death in bilharzic cirrhosis. Patients with Schistosoma mansoni infection may present a clinical picture that differs in many respects from that of hepatic cirrhosis due to other causes. The exact role that the parasite plays in the production of this clinical picture remains to be elucidated.

Transient Seropositive Non-Syphilitic Pneumopathies: (Fanconi-Hegglin's Syndrome). T. Cerviá and A. Méndez de Lugo. Rev. clín. españ. **57:**352-356 (June 30) 1955 (In Spanish) [Madrid, Spain].

This syndrome consists of bronchopulmonary symptoms, roentgen signs of pulmonary inflammation with perihilar infiltration, and a positive Wassermann reaction in nonsyphilitic persons. All the symptoms and signs disappear together with the

rapid reversibility of the reaction for syphilis. In the subject of this report, the disease developed in the course of an epidemic bronchopulmonary disease. The patient had no syphilis. She had a healed pulmonary tuberculosis. The clinical symptoms, roentgen signs, and positive results of the Meinicke and Sachs-Witebsky's reaction reverted to negative within a week from first consultation. The treatment during this week consisted of administration of penicillin in daily doses of 800,000 units, 0.5 gm. of streptomycin and 1 gm. of ascorbic acid. The reaction for syphilis continued negative for the three weeks the patient was under observation, after it had reverted from a week of positive results. The authors point out that, although the syndrome is benign and of short duration, the transient positive results of tests for syphilis embody a medicosocial significance. Duration of the syndrome is three to eight weeks. The false positive results of the reactions for syphilis are due to the dysproteinemia of the globulin fraction that, latent or evident, exists in certain types of pulmonary inflammation and manifests itself by transient changes of the blood serum that are favorable for the production of the false positive test for syphilis.

Use of Lipoid Organ Extracts in Cardiac Therapy. G. Ferrarini and G. Galli. Policlinico (sez. prat.) **62:**794-800 (June 13) 1955 (In Italian) [Rome, Italy].

"Cellulin Coreale," a lipoid extract of myocardium, was given, combined with cardiotonics and cardiokinetics, to 33 patients with heart disease. Electrocardiograms were taken before and after the therapy. The most favorable action of the extract was observed in patients with myocardial hypoxia in whom, in addition to a definite improvement in the subjective symptoms, regression of the signs of myocardial-coronary involvement was seen on the electrocardiograms. The most evident changes were in the ST and T tracings. Results were satisfactory in patients with atrial fibrillation who were given the extract at first combined with quinidine and digitalis and later alone. They were satisfactory also in patients with myocardial infarct to whom the extract was administered with adenosine triphosphoric acid or cocarboxylase after they had overcome the acute period. They were fair in two patients with chronic cor pulmonale and poor in patients with severe cardiovascular decompensation, especially if this was secondary to mitral defects with marked edema and decreased diuresis. Digitalis poisoning, when present, subsided gradually after the administration of this extract, and sensitivity to that drug was restored in the patients who were no longer responding to it. A late follow-up of some of these patients indicated that the good effects continue to be present for a long time after discontinuance of the therapy. The best dose was found to be one to two 1 cc. vials of the extract daily for 15 to 30 days. If necessary, a second course can be given after a treatment-free period of 20 days.

Protein-Bound Iodine—A Newer Aid in Medical Diagnosis: Report of 700 Cases. N. A. Murray. J. Florida M. A. **42:**187-191 (Sept.) 1955 [Jacksonville, Fla.].

Of 700 blood samples on which protein-bound iodine determinations were performed by the author in the course of the last three years, 400 were normal and 300 were abnormal. When the protein-bound iodine value of the serum is determined, a practical blood thyroxin level is obtained. The level of circulating thyroxin would seem to be the most accurate measurement of thyroid function currently available. The determination of serum protein-bound iodine thus offers the most valuable information of any single test in the evaluation of the thyroid status. It is not necessary for the patient to be present while the test is being performed. The protein-bound iodine values for normal persons fall in the range of 3 to 8 mcg. per 100 cc. The elimination of sulfuric acid in the final steps will increase the accuracy of the determination. The reading of the values from a precalibrated graph is not recommended. Determination of protein-bound iodine is a submicro procedure that is simplified by the elimination of some of the time constants and the use of an automatic calculator to derive the final answer. So far as is known at present, an abnormal increase in protein-bound iodine occurs only in hyperthyroidism, in early hepatitis, immediately after thyroidectomy, and in patients receiving certain types of drug therapy. An abnormal decrease in the protein-bound iodine level is noted only during hypothyroidism, hypoproteinemia (nephrosis), and during the administration of certain drugs. Thus the serum protein-bound iodine determination is extremely valuable to the clinician and the surgeon as an aid to the evaluation of patients with hyperthyroidism and hypothyroidism. The following simple protein-bound iodine tolerance test was developed by the author. A fasting protein-bound iodine specimen is drawn; then the patient is given 10 drops of strong iodine (Lugol's) solution. In a euthyroid patient there will be a 400 to 600% increase in the protein-bound iodine level, while in a patient with hyperthyroidism the increase will be less than 100% in 48 to 72 hours. This test will be applied to patients with hypothyroidism in the near future.

Tuberculosis in Persons Vaccinated by BCG Scarification. C. Gernez-Rieux, M. Gervois, C. Voisin and R. Lebeurre. Rev. tuberc. **19:**537-547 (No. 5) 1955 (In French) [Paris, France].

A follow-up study was made of 10,755 persons who had been vaccinated with BCG as school children in the period 1947-1951. For controls, 2,063 persons were drawn from the 1949 list of nonvaccinated school children. Thoracic manifestations of tuberculous primary infection occurred at the rate of 0.32 per 1,000 years of observation among the vaccinated children as compared with 6.47 among the controls. Extrathoracic tuberculosis was notably less frequent and less severe among those vaccinated. There was no case of tuberculous meningitis or osteoarticular tuberculosis among the vaccinated persons. Pleural disease and the ulcerocaseous form in the lungs were five times less frequent among them. It seems that, when tuberculosis does appear in BCG vaccinated persons, it takes benign, easily curable forms.

Antibrucellar Vaccine Therapy in Painful Syndrome of Locomotor Apparatus Due to Brucellosis. R. Verdú. Sem. méd. **62:** 258-264 (Aug. 4) 1955 (In Spanish) [Buenos Aires, Argentina].

The syndrome described by the author consists of pseudorheumatic erratic pain, mainly located in the spine. The patients complain also of occipital headache, loss of memory, dizziness, and auditory, hepatic, and genital disorders. The disease may develop in patients of either sex in rural or in urban zones. Although the syndrome is caused by latent brucellosis, there are neither clinical symptoms nor roentgen signs of brucellosis. Either or both the Huddleson and Burnet's tests give positive results. The diagnosis is made from positive results of a test consisting of an intravenous injection of 1 cc. of Behring's concentrate vaccine that contains 1 billion sterilized Brucella organisms in 1 cc. of the vaccine. Positive results are manifested by aggravation of pain occurring within 3 to 48 hours after administration of the vaccine. Fever may or may not appear. The treatment consists of intravenous injections of 1 cc. each of Behring's vaccine, containing from 50 to 1,000 million sterilized Brucella organisms according to the reaction of the patient. The vaccine is given at weekly intervals for a period of from 4 to 15 weeks, according to the control of pain as reported by the patient. As soon as the patient reports a feeling of well-being immediately after having received the vaccine, the injections are given at longer intervals, first of 10 days and later at monthly intervals for several months. Transient mild pseudorheumatic pain reappears in rare cases several months after discontinuation of treatment. It is controlled by a new series of a few injections of the vaccine. Injections of 1 cc. of Behring's concentrate vaccine for the new series of treatment are given at weekly intervals. Both the test and the treatment are well tolerated and reliable. Three cases are reported.

An Evaluation of the Effect of Continuous Long-Term Anticoagulant Therapy on the Prognosis of Myocardial Infarction: A Report of 82 Cases. M. M. Suzman, H. D. Ruskin and B. Goldberg. Circulation **12:**338-352 (Sept.) 1955 [New York].

At the General Hospital in Johannesburg, South Africa, continuous anticoagulant therapy was given for periods of 3 to 76 months to 82 patients having survived an acute attack of myocardial infarction for three months or more. Another group of 88 patients whose treatment with anticoagulants was limited to

the acute phase of an infarction and who were observed for similar periods, served as a control group. During the acute phase of myocardial infarction, heparin was used initially in most of the patients for periods ranging from one day to three weeks in the dosage that maintained the blood clotting time at approximately twice the normal. A day or two before discontinuing heparin therapy, oral treatment with bishydroxycoumarin (Dicumarol) or phenylindandione was started and discontinued after periods ranging from three weeks to three months in the patients of the short-term group but continued indefinitely in those comprising the long-term group. The weekly maintenance dose of bishydroxycoumarin ranged between 150 and 1,000 mg. and of phenylindandione between 125 and 700 mg., with an average in most of the patients for both drugs of 350 to 450 mg. Prothrombin control was maintained in all patients. The optimum therapeutic range was arbitrarily fixed at a prothrombin index of 40 to 60%. In 70% of the patients the prothrombin level was maintained in the therapeutic range more or less constantly. Wider fluctuations occurred in 20%, and it was necessary to vary the dosage of the anticoagulant from time to time in an attempt to maintain a more constant level. In 10% of the patients the control was considered poor, in that wide inexplicable fluctuations occurred frequently and it was difficult to maintain the prothrombin levels within the therapeutic range. The long-term and short-term groups were compared in respect to mortality, incidence of recurrent infarction, angina, and cardiac failure. Of the 82 patients in the long-term group, 6 died, a mortality rate of 7.3%, and 7 (8.5%) had recurrences of myocardial infarction, whereas, of the 88 patients in the short-term group, 29 died, i. e., a mortality rate of 33%, and 24 (27.3%) had recurrences of myocardial infarction. Separate comparisons were made of mild and severe cases, and when the former were eliminated the long-term group comprised 67 patients, 5 of whom died (a mortality rate of 7%) and 7 had recurrences of myocardial infarction, whereas in the short-term group consisting of 60 patients, 26 died (a mortality rate of 43%) and 21 had recurrences of myocardial infarction. Of the 21 patients with a history of previous infarction in the long-term group, 3 (14.3%) died, compared to 10 (66.6%) of the 15 patients with such a history in the short-term group. The incidence of angina pectoris after the presenting attack of myocardial infarction was approximately the same for both groups, whereas relief or improvement of this condition occurred in 23 (56%) of the 41 patients in the long-term group, compared with 9 (23%) of the 39 patients in the short-term group. Cardiac failure occurred with similar frequency in both groups, but 2 (11.8%) of the 19 patients with this complication in the long-term group died, compared with 8 (57.1%) of the 14 patients with this complication in the short-term group. The authors' findings suggest that patients in whom the presenting attack is mild, in addition to being the first, and who receive short-term anticoagulant therapy show a favorable outlook in respect of subsequent infarction, cardiac failure, and death, irrespective of whether or not the anticoagulant therapy is continued indefinitely. By contrast, the patients most likely to benefit from long-term anticoagulant therapy are those in whom the presenting attack is severe and who also have a history of previous myocardial infarction.

Dissecting Aneurysm of Aorta. G. Omland. Nord. med. **54:** 1251-1255 (Aug. 11) 1955 (In Norwegian) [Stockholm, Sweden].

All but one of the eight cases of dissecting aneurysm of aorta with rupture were in men. The average age was 60 years. Four patients had symptoms of cardiovascular disorders, two had symptoms of hypertension, one had angina pectoris, and one, dyspnea. There was a sudden onset with violent pain in six cases; in two cases the pain increased gradually. Death, which occurred in from three hours to 11 days, was due to rupture of the dissecting aneurysm into the pericardium in seven cases and into the mediastinum in one case. The intimal rupture was located in the ascending aorta or the arch of aorta. The dissecting aneurysm continued in the direction of the heart and, in two cases, also in distal direction along the whole aorta. The etiology is not clear. There must be weakness in the arterial wall, especially in the media. In all cases more or less marked pathological changes were found in the aortic wall. Typical medionecrosis cystica was not established. The pain, most often retrosternal, is usually intense and can radiate in different directions but rarely, if ever, to the arms. As the dissecting aneurysm advances and blocks the vessels to the different organs, cardiac, pulmonary, neurological, gastrointestinal, and renal symptoms and symptoms from the extremities may arise. The most frequent mistaken diagnosis is probably cardiac infarct. Correct diagnosis before death was made in two of the cases described. In most cases the diagnosis was cardiac infarct and the usual anticoagulant treatment was applied. It is likely that anticoagulants may aggravate the prognosis in dissecting aneurysm of the aorta, and it is therefore important to bear the affection in mind in differential diagnostic considerations in cases of doubtful cardiac infarct or embolism.

Diffuse Interstitial Pulmonary Fibrosis: The Hamman-Rich Syndrome. J. C. Sloper and E. Williams. Lancet **2:**533-535 (Sept. 10) 1955 [London, England].

Sloper and Williams present an additional case of the syndrome described by Hamman and Rich in 1944. The patient was a 37-year-old man, who for six years had noticed increasing shortness of breath on exertion. Twelve months before admission, he was unable to walk more than 100 yards without wanting to rest and was forced to give up work. He also complained of palpitations when breathless, with, more recently, attacks of dimness of vision and lightheadedness. An unproductive cough occurred in paroxysms, and, though at first it disappeared for periods of many weeks, it was later persistent and very distressing. Examination revealed slight cyanosis, clubbing of the fingers, increased rate of respiration, and vesicular breath sounds with scattered inspiratory crepitations. A chest radiograph showed fine mottled opacities on a reticular background in both lung fields with doubtful evidence of cardiac enlargement. An electrocardiogram showed the changes of right ventricular preponderance, and a biopsy from the lower lobe of the left lung revealed pathological changes subsequently demonstrated throughout the lungs at autopsy. He became increasingly dyspneic and cyanosed, and signs of congestive cardiac failure in the form of edema, elevation of jugular venous pressure, and hepatic enlargement appeared. There was no response to treatment. He died suddenly during the fifth week. The pathological changes in this case conformed closely with those originally enumerated by Hamman and Rich, who stressed an unusual type of inflammation, eosinophil infiltration, absence from lesions of stainable bacteria, a diffuse and progressive interstitial fibrosis, enlargement of the alveolar lining epithelial cells, necrosis of these and the bronchiolar epithelium, edema and fibrin deposition in the alveolar walls, and the deposition of a hyaline membrane (elsewhere referred to as fibrinous) lining the alveoli. An analysis of the original four cases also reveals that emphysema and alveolar destruction were conspicuous. Now that a number of cases have been reported, it is possible to qualify these criteria. There are three essential abnormalities: (1) the unusual type of the inflammation and the absence of stainable bacteria; (2) the lining of many alveoli by cubical epithelium (i. e., so-called alveolar-cell metaplasia); and (3) diffuse interstitial fibrosis. Two additional changes were conspicuous in the patient here presented: the presence of emphysema (a feature noted in most cases of the disease) and an apparent excess of smooth muscle. This latter feature may serve to differentiate a subgroup of the Hamman-Rich syndrome.

Spontaneous Disappearance of Tuberculomata of the Lung. A. H. Campbell. M. J. Australia **2:**242-245 (Aug. 13) 1955 [Sidney, Australia].

The relatively sudden disappearance of pulmonary tuberculomas is observed sufficiently frequently during the follow-up investigation of tuberculous patients to warrant the conclusion that the disappearance is an important aspect of the natural history of tuberculoma. Among some 2,000 tuberculous patients, predominantly males, attached to the Chest Clinic for outpatient observation, 8 were discovered in whom a tuberculoma had disappeared suddenly. A tuberculoma was defined as a rounded or semirounded lesion at least 1 cm. in diameter, having a defined margin and considered to be tuberculous on bacteriological or

radiological grounds. As there are considerable differences of opinion concerning the treatment of tuberculomas, the author investigated their termination. The eight patients were followed subsequently for between nine months and four years. During this period of observation, seven of the patients have shown no evidence of tuberculous activity attributable to the original lesion or its evacuation. In the seven cases in which the phenomenon was harmless, there was a uniform lengthy period of quiescence of the tuberculomas prior to their disappearance. It is postulated that the lesions were evacuated after the tubercle bacilli had perished or become nonviable. The phenomenon appears to be a final phase in the natural history of tuberculomas, and occurs sufficiently frequently to warrant a critical reappraisal of the policy of resecting tuberculomas and other closed lesions.

Drug Therapy in Hypertension with Hemorrhagic Hypertensive Retinitis. C. F. Burnett Jr. and J. A. Evans. New England J. Med. **253:**395-398 (Sept. 8) 1955 [Boston].

Patients with grade 3 and 4 hypertension were subjected to drug therapy. To exclude patients in the terminal stages of the disease, the authors did not include in this report the patients treated for less than four months. Patients selected for treatment with the potent drugs were first treated with Rauwolfia serpentina (Raudixin), in doses of from 50 to 100 mg. three times daily, or with reserpine (Serpasil), in doses of from 0.1 to 0.25 mg. three times daily, for periods of from three to six weeks at home. After this period of priming with Rauwolfia serpentina, the patients were hospitalized and one of the autonomic blocking agents was added. Earlier the authors used hexamethonium by injection or oral administration, but, since the advent of pentolinium (Ansolysen), they have largely abandoned hexamethonium because of the more prolonged and predictable effect of pentolinium. By priming the patients with Rauwolfia serpentina, it was possible to use smaller doses of the blocking agents with fewer side-reactions and smoother blood pressure curves. None of the 78 patients with severe grade 3 or 4 hypertension showed adequate response of the blood pressure in this priming period. Since pentolinium with its more predictable intestinal absorption became available, it has been possible to control the pressure more adequately without the danger of serious hypotensive reactions. This therapy is begun with 10 mg. four times daily before meals and at bedtime, and then the dosage is increased or decreased. The patients are taught to take their own blood pressures and to plot them on graph paper, the graph revealing the trend of the blood pressure. Usually the patient can be discharged in 12 to 14 days. Of 56 patients with grade 3 hypertension who were treated from 4 to 31 months, 53 experienced a significant drop in blood pressure and 34 showed improvement in the fundi, with absorption of hemorrhages and exudates. Forty-two of the original 56 patients are alive. Twenty-two patients with grade 4 hypertension were treated, and 16 showed a significant drop in blood pressure. Thirteen of the 22 patients survived. The principal cause of death was uremia, with cerebrovascular accidents a close second. Myocardial infarction, congestive heart failure, and hypertensive encephalopathy accounted for the remainder. The drugs are not without danger unless the dose is carefully controlled. One can best accomplish this by beginning treatment in the hospital and by teaching patients to take and record the blood pressure at home.

Rauwolfia Serpentina Treatment of High Blood Pressure. R. J. Vakil. Acta med. scandinav. **152:**107-114 (No. 2) 1955 (In English) [Stockholm, Sweden].

Of 100 patients with essential benign hypertension, 50 (group 1) were treated with the powdered root of Rauwolfia serpentina in tablet form, 25 (group 2) with reserpine, 13 (group 3) with the powdered root of Rauwolfia serpentina and veratrum viride, and 12 (group 4) with the powdered root of Rauwolfia serpentina and hexamethonium. The dose schedules observed were as follows: in group 1, one tablet of the powdered root (equivalent to 4 mg. of total alkaloids) three times daily; in group 2, one tablet containing 0.5 mg. of reserpine twice daily; in group 3, one tablet of the powdered root three times daily and 10 mg. of alkavervir (Veriloid) daily; in group 4, one tablet of the powdered root three times daily with 250 mg. of hexamethonium chloride given orally. Each patient was given first a four weeks course, then treatment was discontinued for two to four weeks (withdrawal phase) and was reinstituted and maintained for two to six months (second course). After one week of treatment the average drop in systolic blood pressure was 9 mm. in group 1, 11 mm. in group 2, 16 mm. in group 3, and 22 mm. in group 4; corresponding falls in diastolic blood pressure were 4 mm., 4 mm., 8 mm., and 13 mm. respectively. Besides lowering of blood pressure, subjective improvement was noted in 85 to 90% of the patients in group 1 and 2, in 61% of the patients in group 3, and in 67% of the patients in group 4. The results obtained with the powdered root and with reserpine were similar concerning hypotensive response and persistence and consistency of action and side-effects. With the addition of veratrum viride and hexamethonium to Rauwolfia serpentina, the hypotensive response was prompter, more intense, and less sustained; subjective improvement was less noticeable; and unpleasant reactions were more frequent. Results obtained in the author's patients suggest that Rauwolfia serpentina is a useful but mild hypotensive agent, capable of lowering both systolic and diastolic blood pressure, free of serious side-effects, easy to administer, and applicable to most patients with hypertension. It, therefore, deserves a definite place in the treatment of hypertension. While most patients with mild or moderate degrees of hypertension, and particularly of labile type, are amenable to and suitable subjects for treatment with Rauwolfia serpentina alone, those with more severe forms of hypertension, particularly when associated with fixed levels of blood pressure, may obtain better results with combined treatment.

Newer Drugs in the Treatment of Hypertension: II. Use of Hexamethonium in Combination with Hydralazine. C. L. Rast and E. S. Orgain. Circulation **12:**361-369 (Sept.) 1955 [New York].

Combined treatment with hexamethonium and hydralazine for periods of from 5 to 22 months was given to 61 patients between the ages of 15 and 65 years with severe hypertensive vascular disease, including 9 patients with malignant hypertension. Fifty-one patients were hospitalized for one to six weeks, and 10 were treated on an outpatient basis. Most of the patients were treated orally; parenteral therapy was reserved principally for patients with malignant hypertension, significant evidence of arterial disease, or impairment of renal function. During combined therapy, the dose of hexamethonium ranged from 0.75 gm. to 4.75 gm. per day with an average dose of 1.8 gm. per day. The dose of hydralazine ranged from 75 mg. to 1,100 mg. per day with an average dose of 418 mg. per day. Ten months was the average duration of treatment per patient. In 46 (76%) of the 61 patients definite reduction in recumbent blood pressure (drop in mean recumbent blood pressure of 20 mm. Hg or greater) was achieved and maintained throughout the treatment, and approximately 40% of the patients treated in the late follow-up period showed good control of recumbent blood pressure (average recumbent pressure 160/110 mm. Hg or lower). No tendency for initial blood pressure reduction or control to be lost was observed. When hydralazine was added to hexamethonium in 31 patients who had been treated with hexamethonium alone for periods of from 5 to 26 months (average 10 months), further reduction in mean blood pressure and more satisfactory control of recumbent blood pressure were achieved in most patients. The late addition of hydralazine to hexamethonium produced equally good eventual blood pressure reduction and control as did the initial combination of the two drugs; in the latter instance, however, better results in the course of combined treatment were achieved earlier. Improvement in retinopathy and in the electrocardiogram occurred in one-fifth of all patients in the course of combined treatment, while little appreciable effect on renal function or heart size was noted. Vascular complications incident to the hypertensive process were not prevented by the combined therapy. Seven patients (11%) died, but only one death was attributed to the drugs. Six nonfatal complications, such as coronary insufficiency, myocardial infarction, congestive heart failure, and cerebral thrombosis, also appeared in the course of the treatment. Late systemic reactions to hydralazine were observed in seven patients (11%); in one

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patient the illness simulated disseminated lupus erythematosus and necessitated administration of corticotropin and cortisone. Combined treatment with hexamethonium and hydralazine together with rigid dietary restriction of sodium constitutes at present an effective form of treatment for malignant hypertension and severe essential hypertension when renal function is good. The hazard of late systemic reactions to hydralazine [*J. A. M. A.* **157:**894 (March 12) 1955] limits the usefulness of this drug in the long-term therapy of hypertension.

Prevention of First-Attack Rheumatic Fever. J. P. Hubbard. Ann. Int. Med. **43:**504-510 (Sept.) 1955 [Lancaster, Pa.].

Efforts are being made to prevent rheumatic fever and bacterial endocarditis through control of streptococcic infections. The campaign is twofold: to prevent first-attack rheumatic fever in the general population and to prevent recurrent episodes in individuals who have already had a first attack. Prophylactic measures directed toward the second of these objectives have now become well established, but the prevention of first-attack rheumatic fever in the general population is a newer concept. The American Heart Association Committee on Prevention of Rheumatic Fever and Subacute Bacterial Endocarditis states that 3% of untreated streptococcic infections in the general population are followed by rheumatic fever. It is suggested that adequate and early penicillin treatment will eliminate streptococci from the throat and will prevent most attacks of rheumatic fever; therefore, when streptococcic infections occur, penicillin treatment should be started immediately and effective blood levels maintained for at least 10 days. Community programs intended to prevent first-attack rheumatic fever through control of streptococcic infections among school children have been started. The essential feature of these programs is the culturing of the throats of children suspected of having streptococcic infections and the treating of those whose throat cultures have been found to be positive for Streptococcus. The author reviews some of these programs, particularly that of Youngstown, Ohio, and discusses some of the questions raised by such programs. He concludes that, for the prevention and control of rheumatic fever, all respiratory infections should be given serious attention, particularly among children of school age, since this is the period when the incidence of first attacks of rheumatic fever is highest. For the present, until further experience has accumulated, it seems best to reserve judgment on the efficacy and practicality of programs involving mass culturing of the throats of school children. But in private practice, in the hands of a skillful physician, streptococcic infections can often be recognized clinically on the basis of characteristic symptoms and signs. For such patients, penicillin therapy may be started without waiting for bacteriological confirmation. The less impressive respiratory infections, which may also be due to the hemolytic streptococci and which, if untreated, may also lead to rheumatic fever, are a more difficult problem. In such cases bacteriological examination is of greatest value in order that penicillin therapy may be started promptly in those cases that are of streptococcic origin, while, at the same time, unnecessary medication may be avoided for those patients who do not show evidence of streptococcic infection.

Current Status of the Control of Influenza. T. Francis Jr. Ann. Int. Med. **43:**534-538 (Sept.) 1955 [Lancaster, Pa.].

The fact that influenza was not a simple disease immunologically was demonstrated by the studies of 1937-1938, which disclosed the variation in strains of the virus that had first been identified in 1933-1934 and was subsequently called Type A. In 1940, Type B virus was identified; in 1950, a virus recovered by Taylor a year earlier was shown to be of epidemic character and was called Type C influenza virus. More recently a virus isolated in Japan in 1952 has been shown on serologic evidence to be prevalent in this country, and it may be influenza D. These represent major, distinct immunologic types without evidence of cross immunity. But the differences between strains of Type A and Type B also may be sufficiently sharp that cross immunity is not obtained. Illustration of this fact occurred in 1947 when the strains called A-prime appeared. Immunity to the strains identified earlier did not protect against these mutants, although the latter could be readily shown to contain antigens also present in the earlier strains. The fact that changes in composition of virus strains can be steadily expected has led to the suggestion that vaccination is not a practicable method of prevention. The counter proposal is that the strains of virus belonging to Type A, for example, possess a large number of antigenic components, varying primarily in quantity or in different degrees of prominence among the antigens. On this basis, strains of virus containing significant quantities of the requisite components may be selected so as to provide adequate amounts of all the constituent antigens and thus furnish all the antigens of which that type of virus is composed. Recent studies even indicate that strains may be manipulated experimentally to alter the antigenic dominants, suggesting, thereby, that the necessary components for a complete vaccine can be arranged. The results of studies in vaccination with inactive influenza virus vaccine demonstrate its high effectiveness. Reactions are few, but the vaccine should not be given to persons naturally sensitive to eggs or chickens. The wider use of the vaccine seems desirable, and it may sharply reduce the risk of influenza and of other respiratory disorders that may accompany or follow it.

Defective Serum Gamma Globulin Formation. T. H. Brem and M. E. Morton. Ann. Int. Med. **43:**465-479 (Sept.) 1955 [Lancaster, Pa.].

Agammaglobulinemia has been seen most frequently in young boys but has also been observed occasionally in adults. The characteristic of this anomaly is the inability to elaborate gamma globulin, including antibodies, and the consequent marked susceptibility to infections, although all other serum protein fractions are normal. The authors cite histories of seven patients, all males, in whom gamma globulin was not demonstrable electrophoretically. Six of them were adults when the anomaly was discovered, although in two of them the manifestations began during childhood. The seventh is a boy, now 12 years old. The clinical manifestations of the anomaly vary considerably in this series, and the cases fall roughly into three categories. In three of the patients, lymphadenopathy and splenomegaly were prominent features, and the diagnosis of giant follicular lymphoma was either made or entertained on lymph node biopsy. One of them died, but no evidence of lymphoma was found on postmortem examination. The other two show no evidence of progressive lymphomatous disease. Both of these have advanced liver disease as a result of chronic hepatitis. Two patients, although devoid of serum gamma globulin on electrophoretic examination, possessed isohemagglutinins, and were not unusually susceptible to infections. No underlying or concomitant organic disease was detected. These two cases may have a milder degree of the same fundamental defect. The other two patients were brothers, both of whom had long histories of respiratory infections. Chronic lymphocytic leukemia developed late in life, and subsequent electrophoretic examination of their serum proteins revealed no gamma globulin. This is very rare in leukemia and is probably coincidental rather than a result. The pathogenesis of agammaglobulinemia is obscure, but it has been suggested that there are two mechanisms, the one operating in children being hereditary and the other creating the defect in adults being acquired. The occurrence of the anomaly in siblings, reported here for the first time, lends support to the hypothesis that it is genetically determined even when appearing in adults. The demonstration of absence of isohemagglutinins and an unexpectedly slow erythrocyte sedimentation rate are helpful tests when the defect is suspected. Although the defect appears to be permanent, its effects may be ameliorated by the administration of gamma globulin and the use of antibiotics.

Gamma Globulin-Deficiency Disease. G. Heuchel and D. Jorke. Medizinische, no. 35, pp. 1181-1186 (Aug. 27) 1955 (In German) [Stuttgart, Germany].

Three typical cases of agammaglobulinemia are described in a 23-year-old man and in two women, aged 25 and 32 years respectively. Serum protein determinations by means of electrophoresis revealed extensive reduction or complete absence of the gamma globulin fraction. The patients presented a pronounced tendency to recurrent infections. These two diagnostically decisive characteristics emphasize the condition as a disease entity for which the term gamma-globulin-deficiency disease is sug-

gested. Phases of hypogammaglobulinemia alternated with those of complete agammaglobulinemia in the male patient, who had 16 attacks of pneumonia in the course of four years. The two women also had frequent recurrences of pneumonia. The disease was considered congenital in all three patients, since history of repeated infections could be traced back to infancy; in the man it was considered hereditary, since the patient's younger brother also had hypogammaglobulinemia and a tendency to infections. The total serum protein values varied from 5.30 to 7.72%. The erythrocyte sedimentation rate was first increased in the course of pneumonia and was rapidly restored to normal when the pneumonia subsided. The various other serum colloid reactions yielded normal results. The alpha and beta globulin fractions were only slightly increased. Antibiotic therapy was followed by prompt clinical response, but resistance to penicillin, which developed in one of the female patients as a result of repeated therapeutic courses with this drug, made the use of the broad spectrum antibiotics necessary. Although continued treatment with gamma globulin has the disadvantage of its high price, this type of therapy was instituted recently in two of the authors' patients. It is still too early to evaluate the results. The general condition of the patients was improved by repeated transfusions of fresh blood at short intervals, but the gamma globulin fraction remained absent in the patients' serums.

SURGERY

Management of Massive Hemoptysis, Not Due to Pulmonary Tuberculosis or Neoplasm. J. L. Ehrenhaft and R. E. Taber. J. Thoracic Surg. **30:**275-287 (Sept.) 1955 [St. Louis].

Of 12 patients between the ages of 38 and 69 years with massive hemoptysis admitted to the surgical service of the State University of Iowa Hospitals during the last five years, bronchiectasis of mild degree was the cause of the massive bleeding in 2, broncholithiasis or calcified peribronchial lymph nodes in 6, and no specific cause for the massive bleeding could be found in 4. None of these patients had a malignant or tuberculous disease. The authors believe that massive hemoptysis constitutes an indication for thoracotomy as soon as localization of the bleeding site has been established. Preoperative diagnostic procedures for localization include chest roentgenograms, bronchography with the aid of instillation of iodized oil (Lipiodol) during quiescent periods, and bronchoscopy carried out during the active bleeding. The visualization of calcific peribronchial nodes in the chest roentgenogram appeared to be very significant. Although the source of bleeding may not be visualized directly by bronchoscopy, it may be possible to determine the lobe or occasionally the segmental bronchus from which the blood is coming. Removal by suction of endobronchial clots is essential. The preoperative bronchoscopic indication of the site of bleeding will give additional assurance to the surgeon and will help in the decision as to the extent of resection to be carried out. It will prevent unnecessary sacrifice of pulmonary tissue since operative findings in themselves are often misleading. In the authors' patients, broncholithiasis or calcific peribronchial lymph nodes were found to be one of the more frequent causes of massive pulmonary bleeding. Of the 12 patients, 2 had left upper lobectomy, 2 left lower lobectomy, 1 right lower lobectomy, 2 right upper lobectomy, 2 lingulectomy, 2 left pneumonectomy, and 1 enucleation of a calcific peribronchial node embedded within the membranous portion of the left mainstem bronchus, without pulmonary resection. There was no significant morbidity and no mortality in the 12 patients. Recent communications from each of them indicated that there have been no further bleeding episodes.

Spontaneous Rupture of the Esophagus, with Presentation of Four New Cases. G. W. B. Starkey. J. Thoracic Surg. **30:**300-315 (Sept.) 1955 [St. Louis].

The occurrence of so-called spontaneous rupture of the esophagus is reported in three men and one woman of the ages between 45 and 75 years. Three of the four patients had esophageal rupture associated with severe vomiting, the fourth with yawning and stretching. It would appear that a sudden increase in intra-abdominal and therefore intragastric pressure was a basic factor in three patients. Spontaneous rupture of the esophagus occurred in normal esophagi in all four patients; this observation, as well as a brief perusal of the literature, suggests that spontaneous perforation of the esophagus in patients with known esophagitis is a most unusual occurrence. In not one of the four patients was the initial diagnosis correct, although it is usually easy to make. Severe pain in the anterior and posterior chest and a shock-like picture preceded by violent vomiting or effort are suggestive of rupture of the esophagus. The presence of supraclavicular and mediastinal emphysema and fluid or fluid and air in either pleural space is almost diagnostic. A swallow of 10 to 20 cc. of iodized oil (Lipiodol) preceding the roentgenogram almost invariably shows the leak in the esophagus. The delays from the time of rupture until surgical intervention varied from 12 hours to eight days. Three patients were treated by primary closure of the esophageal tear, and two of them survived. The third patient, aged 75, died on the fifth postoperative day of a second myocardial infarct. The fourth patient, aged 69, in whom pleural drainage was instituted eight days after the rupture occurred, died three weeks later of massive hemorrhage and perforation of a duodenal ulcer. Treatment in the first 36 to 48 hours after the rupture should consist of surgical closure of the tear with interrupted fine silk sutures and adequate drainage of the mediastinum and pleural space. Massive antibiotic therapy and rapid reexpansion of the lung on the affected side are essential in avoiding late septic complications. Patients seen 36 to 48 or more hours after rupture should be treated by pleural and mediastinal drainage; in addition, a feeding jejunostomy is important for alimentation over the prolonged period of recovery.

Use of Temporary Artificial Shunt in Experimental Surgery of Descending Aorta. F. Caluzzi, E. Fava and E. Perazzo. Minerva cardioangiol. **3:**293-301 (June) 1955 (In Italian) [Turin, Italy].

Autoplastic grafts were performed on the thoracic aorta of two groups of dogs. In the first group, the aortic circulation was interrupted for from 45 to 60 minutes, the time required to suture the graft. Most of the dogs died, and at autopsy severe degenerative changes were found in the kidney, liver, and nervous tissue of the lumbar and sacral regions. Thus, unless there is a well-developed collateral circulation, it is not possible to interrupt the aortic circulation for the time necessary to perform a graft. In the second group of dogs, the authors used a method that enabled them to maintain the continuity of the blood flow through the descending aorta while they sutured the graft. A 4 cm. segment of the aorta was resected, and the autoplastic graft to be inserted was placed over a glass tube, 5 to 7 cm. in length, which was inserted into the aorta and anchored at both ends with umbilical tape. The arterial graft was sutured at both ends all the way around. The tube was then removed through a longitudinal incision made on the anterior side of the lower segment of the aorta immediately below the distal extremity of the shunt. Ten of the 15 dogs survived the operation. Histological studies made on some of them 10 days after the intervention did not reveal alterations in the renal and hepatic parenchyma and the nervous tissue of the lumbar and sacral regions. The authors' technique is easy to perform and promises to give good results, especially in the treatment of coarctation of the aorta.

Morphological and Functional Study on Experimental Liver Regeneration After Partial and Repeated Hepatectomies with Regard to the Regenerative Process in Hepatic Injury and to the Possibilities for Exeresis of the Organ. M. Mancuso and G. Del Grande. Policlinico (sez. chir.) **62:**161-188 (June) 1955 (In Italian) [Rome, Italy].

The regenerative capacity of the liver was studied in two groups of dogs. In the first group of five, 65 to 70% of the liver parenchyma was removed in one stage by resecting the middle and the right lobes after the pedicles had been isolated and ligated and the gallbladder had been removed. Four of the dogs died. In the second group of 15 dogs, the operation was per-

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formed in two stages with removal of the left lobe and, 15 days later, the right lobe; the left lobe with the right lower lobe and, 15 days later, the residual right lobe; or the left lobe with one of the secondary middle lobes and, 15 days later, the right lobe. At the time of the second operation, the liver was already markedly hypertrophied. About two months later the dogs were killed, and the liver was found to have reached and sometimes surpassed the initial weight. This finding indicates that removal of 50% of the liver is well tolerated. The portal pressure was slightly increased in the immediate postoperative period (20 to 30 mm. of water), but this increase was only temporary because at the time of the second operation, or when the dogs were about to be killed, it was only 10 to 15 mm. of water greater than the initial value. The results of liver function tests were negative. The total serum proteins were decreased soon after the operation but in time they returned to normal. The same was true of the albumin-globulin ratio. From the morphological standpoint, the liver assumed the aspect of the human liver because of the marked increase in the volume of the residual lobes. Angiography revealed a normal vascular structure. The architecture of the lobules was normal after regeneration had occurred. Congestion of the sinusoids was marked, especially after the second hepatectomy. This study confirmed the fact that the regenerative processes are located at the periphery of the lobules. It also seemed to support the hypothesis that the biliary ducts contribute greatly to the regenerative process because the regenerative aspects of the parenchyma were observed quite often near the biliary canaliculi. The marked difference in the death rate of the animals of the first group and those of the second group suggests that hepatectomy with removal of more than 50% of the parenchyma at one time is not well tolerated.

New Bouts and Relapses After Pulmonary Resection for Tuberculosis: Study of 1,260 Operations. M. Bérard, R. Arribéhaute, J. Germain and J. Dumarest. Rev. tuberc. **19:**511-536 (No. 5) 1955 (In French) [Paris, France].

An unfavorable light is cast on the good results of surgical treatment of pulmonary tuberculosis by the fact that the disease recurs in some patients. Fortunately, this percentage is small, as shown in the present series of 1,260 resections among which there were 79 recurrences (6.5%). The number of cases in which the disease progressed on the same or opposite side in spite of operation was small. This, together with the fact that old lesions regressed totally or partially, speaks well for the effect of exeresis on the remaining parenchyma. The mechanism of this effect is twofold: suppression of bronchial dissemination and overloading of venous blood, which is unfavorable to the development of tubercle bacilli. It remains true that bed rest and antibiotic therapy, whether associated or not with pneumoperitoneum, materially reduce the number of postoperative progressive bouts of disease.

Pheochromocytoma as a Massive Abdominal Tumor. B. P. Colcock and J. E. Hull. J. Indiana M. A. **48:**955-957 (Sept.) 1955 [Indianapolis].

An instance of an enormous mass that filled the entire abdominal cavity is described in a 50-year-old man. The mass had a cystic consistency to palpation and was smooth and nontender. The patient did not present the clinical picture of hypertension or hypermetabolism; his only symptoms were those secondary to the enormous size of the tumor that extended to within a few centimeters of the pubis inferiorly, to the costal margins superiorly, and more to the left than to the right. A tentative diagnosis was made of a cyst arising from the left lobe of the liver or pancreas. Laparotomy was performed and a cyst was found that filled the entire abdomen. Approximately 4,000 to 5,000 cc. of a brownish-red mucinous fluid was aspirated from the center of the cyst cavity. After the division of many large vessels, the base of the cyst was isolated and was found to be intimately associated with the left renal pedicle. It was necessary to ligate one large branch of the left renal vein, but a smaller branch of the vein and the renal artery were preserved. There was no change in color of the left kidney and it was not removed. The tumor mass was removed intact; it weighed 3,600 gm. (8 lb.). During the final phase of the dissection, an unexplained tachycardia occurred. The blood pressure, which throughout the early part of the procedure had been 150 mm. Hg systolic and 80 mm. Hg diastolic, rose to 210 mm. Hg systolic and 140 mm. Hg diastolic. Soon after the removal of the cyst, the blood pressure returned to normal. The postoperative course was uneventful. The histopathological diagnosis was pheochromocytoma with foci of ganglioneuroma. No evidence of malignant degeneration was found. At one pole of the tumor there was a flattened yellow organ that microscopically proved to be the adrenal gland. Pheochromocytoma may present as a massive abdominal tumor with no associated hypertension or history to suggest this diagnosis. It should be suspected if at operation the tumor appears to arise from the region of the left renal pedicle and particularly if manipulation of the tumor is associated with a hypertensive episode. The tumor removed in the authors' case is believed to be one of the largest pheochromocytomas recorded.

Results of Splanchnicectomy on Patients with Hemorrhagic Hypertensive Retinitis. I Huntington and J. A. Evans. New England J. Med. **253:**398-403 (Sept. 8) 1955 [Boston].

The survival rate up to 10.5 years was determined in 206 patients who underwent sympathectomy and splanchnicectomy, all of whom had hemorrhages in the fundus oculi (grades 3 and 4 hypertension). Although the first patient was operated on 19 years ago and the longest survival is 14.5 years, statistically reliable figures exist for only 10.5 years. Patients with hemorrhagic fundi were selected for study, because they most truly demonstrate the value of the operation. The survival rate after operation in patients with grade 3 and 4 hypertension was compared with the expected survival rate for medically treated patients before the advent of the new hypotensive drugs. In the patients with grade 3 disease, the cumulative survival rate was 46% in 10.5 years, compared with an expected survival rate of 0% according to Keith, Wagener, and Barker. In the patients with grade 4 disease, the relative survival rate was 39.9% in 6.5 years, compared with an expected rate of 5.6%. At 10.5 years, the survival rate was 33.4%. The operative mortality was 2% in the patients with grade 3 and 6% in those with grade 4 hypertension. Seventy-four per cent of the survivors among the former and 75% of those among the latter felt well. Blood pressure was reduced to a satisfactory level in 67% of survivors with grade 3 and 81% of those with grade 4 disease. Cardiac status in patients with enlarged hearts or abnormal electrocardiograms was improved in approximately half the cases of grade 3 and about a third of those of grade 4 hypertension. Hemorrhages in the fundi disappeared in 84% of patients with grade 3 disease, and papilledema and hemorrhages disappeared in 100% of those with grade 4 hypertension Ability of the kidneys to concentrate urine to a specific gravity of at least 1.020 is apparently the best prognostic test for a good result in these two groups. In spite of the advent of more efficacious hypotensive drugs than have hitherto been available, splanchnicectomy is a valuable resort in hypertensive patients with hemorrhages in the fundus oculi.

Acute Gastrointestinal Ulcers After Operations. H. J. de Ruiter. Nederl. tijdschr. geneesk. **99:**2186-2189 (July 23) 1955 (In Dutch) [Haarlem, Netherlands].

The four patients in whom ulcers developed after operations ranged in age from 58 to 78 years. In three of the patients the peptic ulcer was confirmed at autopsy or gastric resection. The fourth patient recovered, but the symptoms of this woman, who had undergone a cholecystectomy, were so typical that the development of an acute peptic ulcer could not be doubted. The other three patients, who died within a month after their operation, had undergone surgery on the urinary bladder (for calculus), on the biliary passages, and on the prostate respectively. The history of a fifth patient, who was operated on for a large inguinal hernia, demonstrated that an existing peptic ulcer may be activated as the result of surgical treatment. It is

suggested that these acute ulcers are simply the result of the exposure of the body to stress during and after the operation. Stress stimulates the body's secretion of acid and pepsin by way of a humoral mechanism involving the pituitary-adrenal axis. The administration of corticotropin or cortisone can have the same effect.

Treatment of Carcinoma of the Thyroid with Radioactive Iodine: (Contribution to Development of Iodine-Thyroid-Problem in Surgery). E. Ruckensteiner. Beitr. klin. Chir. **190:**134-145 (No. 2) 1955 (In German) [Munich, Germany].

In the course of 20 months, 14 patients with malignant goiters were examined at the surgical clinic of the University of Innsbruck, Austria, concerning their suitability for treatment with radioactive iodine (I^{131}). Of 10 patients who were excluded from this type of treatment because of the inability of their tumors to take up I^{131}, 5 had undifferentiated carcinoma of the thyroid, 2 sarcoma of the thyroid, one Langhans' goiter, one hemangiopericytoma, and in one the diagnosis could not be established microscopically. This last patient with a giant tumor that had perforated through the skin was treated by roentgen irradiation alone, while the nine other patients underwent surgical treatment and roentgen irradiation. Of the remaining four patients who were treated with radioactive iodine, the uptake test was negative in two. These two patients, who were given a therapeutic dose of 60 mc. of I^{131} each, despite the negative uptake test, were therapeutic failures. One of these two patients, a 38-year-old woman, was subjected to thyroidectomy three times in the course of 12 years; at the last operation an adenocarcinoma of the thyroid with metastases to the lungs was found, and the patient died three months after the ineffective administration of I^{131}. The other patient, a 63-year-old woman, had a goiter for 20 years that suddenly started to grow rapidly. Roentgen irradiation as well as administration of I^{131} failed; surgical intervention, which was carried out to prevent death from asphyxia, revealed a sarcoma, and the patient died within a few days after the operation. Treatment with radioactive iodine was effective in the remaining two patients. The first of the two, a 43-year-old woman, underwent thyroidectomy four times in the course of 10 years. An adenocarcinoma was detected at the last operation, and three months later the patient again had dysphagia, dyspnea, and cyanosis. Pulmonary metastases were revealed by roentgenologic examination. An uptake test dose of 100 mc. of I^{131} was given, 25% of which accumulated in the neck and the lower area of the thorax. The patient then was given two doses of 50 mc. each on two successive days. Dyspnea subsided within 14 days; roentgen examination six months later showed considerable regression of the pulmonary metastases. The circumference of the neck was reduced by 3 cm., and the patient no longer was cyanotic; she remained free from complaints for 15 months after the operation. The second patient, a 40-year-old woman, underwent thyroidectomy for nodular goiter twice in the course of 22 years. Restlessness, insomnia, loss of weight, pain in the region of the heart, and severe dyspnea were associated with the recurrence of the goiter in the left side of the neck. Postoperative uptake studies showed accumulation of I^{131} in the left side of the neck, and the patient was given 120 mc. of I^{131} 14 days after the operation. One year after the operation she was entirely well, had gained 11 lb. (5 kg.), the white blood cell count showed 5,500 leukocytes and the basic metabolic rate was −10%. The author agrees with other workers that the treatment with radioactive iodine is not a substitute for surgical and roentgen therapeutic measures in the treatment of malignant disease of the thyroid, but it may occasionally be a valuable adjunct to these methods. Provided that there is sufficient iodine affinity, postoperative treatment with radioactive iodine is indicated when healthy thyroid tissue also has been removed surgically. Preoperative uptake studies are advocated. The therapeutic dose of radioactive iodine then represents a special type of postirradiation. Radioactive iodine does not produce a cure, but palliative success may be impressive in 10% of the cases of malignant goiter, including inoperable ones or those treated after surgical intervention.

NEUROLOGY & PSYCHIATRY

Phenylpyruvic Oligophrenia: New Chemicopathological Findings. V. Ferrari, F. Campagnari and A. Guida. Minerva med. **46:**119-127 (July 11) 1955 (In Italian) [Turin, Italy].

The authors report the results of biochemical studies made on two women, 27 and 36 years old, both mentally retarded, with phenylpyruvic oligophrenia. The condition, which is characterized by encephalopathy and an altered phenylalanine metabolism, was moderate in one patient and severe in the other. Study of the amino acids in the peripheral blood revealed an excess of phenylalanine; this became even more marked after the ingestion of proteins. The concentration of the other amino acids was also greater than normal. An excess of phenylalanine and of other amino acids was present also in the urine and the spinal fluid; here too the abnormal values increased greatly after the ingestion of proteins. The findings in the urine revealed not only an abnormal excretion of the acids linked to phenylalanine but also an excess of true phenolic compounds, which were present in amounts that were at least two times greater than the normal values. The urinary excretion of indole derivatives was also altered; it was increased for most of them (indoleacetic, indolelactic, and other undetermined acids) and decreased for 5-hydroxyindoleacetic acid. These findings suggest that in phenylpyruvic oligophrenia there is not only the specific alteration in the metabolism of phenylalanine and tryptophane but also a more general disturbance in the metabolism of the amino acids. The results of the liver function tests were normal.

Psychiatric Complications of Mitral Surgery: Report of Death After Electroshock Therapy. E. L. Bliss, W. R. Rumel and C. H. Hardin Branch. A. M. A. Arch. Neurol. & Psychiat. **74:**249-252 (Sept.) 1955 [Chicago].

Two patients who underwent surgical treatment of mitral valvular disease had schizophrenic reactions postoperatively. They were treated with electroconvulsion. The first patient responded dramatically and rapidly recovered. The second developed a respiratory arrest after the third treatment and died. Thereafter the records of 37 patients who had mitral surgical operations were reviewed; these two patients were among that number. Besides the two full-blown reactions, one of which appeared on a background of previous schizophrenia, short-lived schizophrenic reactions after surgery appeared in two other patients. In one delusions were prominent, while the other reported auditory hallucinations in the absence of confusion or disorientation. One patient had a clearly defined reaction characteristic of an organic confusional state; he was disoriented and confused for three days. Another had a similar episode, but pertinent information on the record was insufficient. Six patients, though not psychotic, were sufficiently anxious and depressed to be mentioned by physicians and nurses. There is reason to ask whether mitral operation may be a greater psychological threat than other major surgical procedures and to question whether chronic rheumatic patients may be particularly vulnerable under these circumstances.

Jaundice Occurring During the Administration of Chlorpromazine. C. H. Stacey, D. W. Huestis, J. G. Howlett and M. M. Hoffman. Canad. M. A. J. **73:**386-392 (Sept. 1) 1955 [Toronto, Canada].

Jaundice developed in 8 of 170 mental patients who were given chlorpromazine by mouth in a dosage varying from 75 to 900 mg. a day. The jaundice was not of the usual hepatocellular type but appeared to be due to obstruction of the intrahepatic biliary tract. Clinically the onset was that of an acute gastroenteritis that persisted for several days. Painless jaundice developed from 16 to 21 days after starting therapy. Hepatomegaly and pruritus were common findings. The biochemical changes included hyperbilirubinemia, hyperphosphatasemia, hypercholesteremia, and negative serofloccculation reactions. Liver biopsy in one case revealed histological features of a progressive intralobular biliary stasis, with a nonsuppurative cholangiolitis. There was no significant change in the parenchymal cells. The general principles of treatment of hepatic

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disease were followed in the majority of patients. Complete bed rest was difficult to obtain because of the associated psychiatric symptoms and mild nature of the hepatitis. The diet was high in calories, protein, and carbohydrate, and low in fat. It was supplemented by vitamin B complex and vitamin C; vitamin K was added when indicated. Pruritus was controlled in most of the patients with calamine lotion. In those patients who were extremely agitated, the lack of bed rest did not seem to affect the course of the disease. Except for one death resulting as a complication of liver biopsy, all the patients eventually recovered. In a group of 100 patients treated with chlorpromazine, the alkaline phosphatase level was determined serially and administration of the drug discontinued when the concentration exceeded normal. Jaundice appeared in only one of these 100 patients. Apparently, if chlorpromazine therapy is discontinued when the alkaline phosphatase level is first found to be elevated, further disturbance in hepatic function can be avoided.

Treatment of Herpes Zoster with Topical Application of Hydrocortisone. F. A. Marshall. J. M. Soc. New Jersey **52:**474-475 (Sept.) 1955 [Trenton, N. J.].

In three patients with herpes zoster, whom Marshall observed in the period of one month, the topical application of a 1% hydrocortisone ointment proved highly effective. Duration of this self-limited disease was symptomatically reduced from weeks to days. The most striking benefit was the amelioration of both pain and skin lesions. Sleepless nights disappeared, and patients could continue their usual occupations within 24 to 96 hours. The ointment was applied twice daily until pain and inflammation had disappeared. No relapses occurred, and no systemic effects or complications were noted.

GYNECOLOGY & OBSTETRICS

Partial Intraligamentary Extrauterine Pregnancy Proceeding to Term, with the Aspect of Acute Abdomen. F. Best and W. Straube. München. med. Wchnsch. **97:**1051-1053 (Aug. 19) 1955 (In German) [Munich, Germany].

A rare case of partial intraligamentary extrauterine pregnancy is described in a 33-year-old woman, who at term was delivered surgically of a normally developed child and who herself survived the operation. An attack of acute abdominal pain associated with sudden bleeding occurred early in the course of pregnancy, and a second attack of subacute abdominal pain occurred three months later. Roentgenologic examination revealed two months before the delivery a normally developed fetus in breech position in the right side of the abdomen. After three days of labor the patient's abdomen suddenly became hard and tense, the pelvis was empty, and the patient was screaming continuously because of most severe cramps. Laparotomy was performed, and on opening of the peritoneum no uterus was observed, but a yellowish green tissue layer that was traversed by many veins the diameters of which reached the size of fingers. Between two of these veins an incision was made causing the explosive escape of yellowish-green amniotic fluid. The arms of the infant were thrown upward from the fetal sac, and the sac became torn deep downward and above the anteriorly situated placenta. Severe hemorrhage resulted, and the mother became pulseless and pale. She was given oxygen, the infant was extracted and cried immediately. Adhesions between the fetal sac and the transverse colon, small intestine, and mesentery were divided, the rectum and the bladder freed, and supravaginal amputation of the uterus was performed. The ovaries and the Fallopian tubes were so deeply embedded that they had to be removed. The patient was given 600 cc. of fresh blood, and the abdominal wall was closed. She received large doses of antibiotics and sulfonamides, and the postoperative course was uneventful. Pathological examination of the uterus, fetal sac, and placenta revealed the remainders of an extrauterine pregnancy that had developed at least partially between the two leaves of the broad ligament. Portions of the broad ligament were found on the upper edge of the anterior surface, in the center of the anterior surface, and in the center of the posterior surface of the fetal sac. Besides a uterine hemorrhage that occurred very early in pregnancy, no signs of intra-abdominal hemorrhage were observed, but there was evidence of peritoneal irritation. The severe pains of the patient at the time of the first episode of acute abdomen were interpreted as rupture of the tubal gestation into the adjacent mesosalpinx. A viable fetus developed between the leaves of the broad ligament. The growing fetal sac acted like an inflammatory tumor in the abdominal cavity, causing repeated peritoneal irritation that reached its culmination when the fetus had proceeded to term. This concept was supported by the presence of adhesions between the fetal sac and the intestine and in the lower abdomen, which made surgical intervention technically difficult. Because of the rarity of this type of ectopic pregnancy, the diagnosis of at least partial intraligamentary extrauterine pregnancy was not made preoperatively, but in the course of the operation only; it was confirmed by the anatomicopathological and microscopic examination of the surgical specimen.

Absence of the Left Diaphragm: An Unusual Complication of Pregnancy and Labor. G. A. Williams and C. F. Whicker. Obst. & Gynec. **6:**272-276 (Sept.) 1955 [New York].

A muscular diaphragm completely separating the abdomen and the thorax is found only in mammals. It is an essential organ of mammalian respiration and as such plays an important part in human reproduction. The increasing size of the abdominal cavity in the later months of pregnancy elevates the diaphragm at the expense of the thoracic cavity, producing minor physiological atelectasis. The diaphragm is also one of the most important muscles used in the voluntary expulsive efforts in the second stage of labor. Any defect, therefore, in the diaphragm may seriously complicate the course of pregnancy or parturition. Diaphragmatic hernias of the esophageal hiatus seldom cause serious trouble and are often asymptomatic, because as a rule only the cardiac portion of the stomach is affected. Hernias of any type, however, that are large enough to permit the escape of other abdominal viscera into the thoracic cavity are potentially grave complications of pregnancy. They disturb the dynamics of respiration and present the dangers of incarceration, strangulation, and perforation common to all abdominal hernias. The intra-abdominal changes of late pregnancy accentuate all of these phenomena, and the expulsive efforts of labor tend to bring them to a critical stage. Discovery of the defect during the first two trimesters should probably be followed by an attempt at repair. Evidence of obstruction, strangulation, or perforation is an indication for immediate surgical treatment at any stage of pregnancy. Arrangements should be made to terminate the pregnancy without allowing voluntary expulsive efforts on the part of the patient. Cesarean section seems to be generally favored, but there is apparently no reason why delivery from below with the aid of forceps should not be satisfactory in the absence of obstetric contraindications. This method was used in a 20-year-old patient whose first pregnancy was successfully managed at the Crawford W. Long Memorial Hospital in 1953. She was delivered of a normal living infant by midpelvic application of Kielland forceps and had a normal and uneventful puerperium. Another patient, seen in 1930, was delivered by cesarean section, but neither she nor her child survived. These two cases, with the 13 previously reported in the literature, make a total of 15 with a mortality of 8. Present methods of management of pregnancy and labor should substantially reduce the high death rate among patients with this unusual complication.

PEDIATRICS

Thrombocytopenia and Giant Hemangioma in Infants. T. A. Good, S. F. Carnazzo and R. A. Good. A. M. A. Am. J. Dis. Child. **90:**260-274 (Sept.) 1955 [Chicago].

Three new cases of thrombocytopenic purpura associated with hemangioma in an 8-week-old boy, a 5-month-old girl, and a 3½-month-old boy are described. Each of the authors' three patients had a large tumor involving the skin as well as subjacent soft tissues; in one patient the tumor occurred on the face

and neck, in another on the leg, and in the third on the thorax. One of the patients died five months after splenectomy, performed in an attempt to allay the thrombocytopenia. The autopsy findings and the terminal clinical course were interpreted as indicating that death was caused by overwhelming sepsis. In the two other patients, the giant hemangiomas were successfully treated. In each of the two patients, the platelet count returned promptly to normal after subsidence of the hemangiomas. In one patient roentgen irradiation to the tumor alone resulted in a cure of both thrombocytopenia and hemangioma. In the other patient, successful treatment consisted of roentgen ray therapy combined with surgical excision of the tumor. Bone-marrow biopsies were performed on each of the three patients. Specimens of the tumor were available in two patients, sections from tissue excised surgically in one of these, and autopsy specimens of the tumor in the third. The bone-marrow studies revealed an essentially normal marrow except for the evidence of response to blood loss, increased numbers of megakaryocytes, and "megakaryocytic arrest" (a shift to the left and little evidence of platelet formation) similar to that seen in essential thrombopenic purpura. Microscopic studies of the hemangiomas showed the occurrence of platelet-thromboses within the vessels of the hemangioma. It is suggested that sequestration of platelets within the tumor accounts for the thrombopenic purpura. In the authors' patients and in those reported on by other workers, it was observed that elimination or destruction of the hemangioma was associated with return of the platelet count to normal, while splenectomy was without effect on the blood dyscrasia. It is postulated, on the basis of these observations, that the thrombopenia and hemangioma are intimately related phenomena in these patients. In essential thrombocytopenia caused by immunologic injury to platelets, the sequestration occurs largely in the spleen, while in the hemangioma-thrombopenia syndrome the major site of platelet destruction is the vascular tumor. Removal of the major site of platelet sequestration might result in a resetting of this homeostatic regulator, thus relieving the megakaryocytic arrest and permitting platelet production. This concept would explain response to splenectomy in essential thrombopenia, as well as the ineffectiveness of splenectomy and the response of thrombopenia after destruction or regression of the hemangioma in the patients with the thrombopenia-hemangioma syndrome. It seems possible that the regulator inducing megakaryocytic arrest may be derived from the platelets themselves in the course of their sequestration or destruction in any part of the body and thus represent a negative feed-back mechanism.

Portal Hypertension in Infants and Children. D. Yi-Yung Hsia and S. S. Gellis. A. M. A. Am. J. Dis. Child. **90:**290-298 (Sept.) 1955 [Chicago].

Of 43 infants and children with portal hypertension seen at the Children's Medical Center, Boston, during the 30-year period from 1924 to 1953, 21 had primary portal hypertension caused by extrahepatic obstructions. A history of omphalitis and sepsis in the course of early infancy, early hematemesis and splenomegaly, the absence of clinical jaundice, and frequent depression of the blood elements were prominent features of this type of portal hypertension. Of these 21 patients, 6 died and autopsies revealed anatomic lesions that could account for the hypertension in the portal system, such as obstructing valves in the lumen of either the splenic vein or the portal veins, or both, and thrombosis and fibrous obliteration of the portal vein just proximal to the entrance into the liver. The 22 other patients had portal hypertension secondary to cirrhosis of the liver. Hepatitis appeared to be the commonest cause, and in many of these patients liver function tests were usually strongly positive. Splenorenal venous shunt appears to be the treatment of choice in children with primary portal hypertension. Since the prognosis of those with secondary portal hypertension appears to be uniformly poor with supportive therapeutic measures such as diet, vitamins, transfusions, paracentesis, and omentopexy, it is felt that venous shunt should also be employed in this group of patients. Ion-exchange resins and a low-sodium diet may be helpful in lowering the mortality associated with shunt procedures.

The Epidemiological Retreat of Tuberculosis: A Ten-Year Survey of Tuberculin Reactors at a Children's Dispensary. K. E. Kassowitz. A. M. A. Am. J. Dis. Child. **90:**283-285 (Sept.) 1955 [Chicago].

Of 8,506 outpatients at the Milwaukee Children's Hospital, between 3 and 16 years of age, who were considered tuberculosis suspects and were subjected to tuberculin testing according to the standard intracutaneous Mantoux method, only 304 had a positive reaction to the test, which is a surprisingly low percentage of 3.5. A breakdown for the last 10 years showed a steady, if somewhat irregular, decline per year from a maximum of 4.7% to a minimum of 3% of reactors, the average for the years from 1944 to 1948 being 3.92%, compared with 3.26% for the last five years. The credit for this gratifying epidemiological regression of tuberculosis may be attributed to some local and some nationwide factors, such as elimination of bovine tuberculosis by way of compulsory tuberculin testing of cattle, improvement in the standard of living and particularly housing, efficient case-finding procedures including routine standard and microfilm chest roentgenograms, tuberculin testing, bacteriological conversion by chemotherapy of large numbers of formerly intractable patients, and BCG vaccination of potential contacts.

Peculiarities of Course and Treatment of Adhesive Pericarditis in Children. S. L. Libov and K. F. Shiryaeva. Pediatriya, pp. 3-9, May-June, 1955 (In Russian) [Moscow, Russia].

The clinical picture of chronic pericarditis in children is fairly characteristic. The changes in venous pressure, electrocardiogram, and roentgenogram are sufficient to confirm the diagnosis, though there may be some patients who are clinically asymptomatic. Three stages of the disease may be differentiated: exudative, transitional, and adhesive (constrictive). The warning signs of cardiac insufficiency usually appear early; incorrect therapy at this time can lead to death within the first weeks of illness, as illustrated by a case report. Decrease in heart volume in exudative pericarditis, accompanied by signs of progressive circulatory insufficiency, gives positive evidence of the formation of adhesions in the pericardium and the conversion of the disease process into the third phase. The resistance of children during the acute stage is less than that of adults. The proper treatment of this pericarditis is surgical and should be performed early, to wit, in the beginning of the period of adhesion formation, in the presence of disturbances in hemodynamics, without waiting for the subsidence of inflammatory signs. When performed in the presence of adequate antibiotic preparation, this operation is completely justified and has a number of definite advantages over late surgical intervention. The best anesthesia to use is intratracheal narcosis. The preferred surgical approach is the transpleural, with wide excision on the left and resection of the fifth or sixth left rib. Resection of that part of the pericardium lying over the left ventricle is advocated, with subsequent interposition of the lung between the heart and chest wall. The beneficial effects of the operation do not appear immediately, but they are more complete and do appear earlier in children than in adults. There is no justification for not operating, even in the presence of severe secondary changes.

So-Called Genital Retardation in Children and Adolescents. J. Vague. Presse méd. **63:**1139-1140 (Aug. 27) 1955 (In French) [Paris, France].

Hormone therapy has recently been used indiscriminately to treat young patients with delayed onset of puberty in whom nothing is radically wrong. Most of them are boys, often with overanxious mothers. They are of three primary types: (1) those with gynecoid obesity that makes the external genitalia appear proportionately smaller, (2) those whose weight is suitable to their height but who tend to be thin and somewhat puerile psychically as well as physically, and (3) those with undescended testes. Thorough examination of each patient is indispensable. Proper diet and passage of time will usually accomplish the

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desired effect. Concerning patients in the last category, it should be remembered that true ectopia, which can only be treated surgically, is rare. Much more often it is a question of an anomaly that will correct itself spontaneously when puberty establishes itself definitively. In girls in whom menstruation has not yet appeared, nothing should be done before the age of 15, and not before the age of 16 if development of the secondary sexual characteristics has taken place by the age of 15. True hypotrophy requiring hormonal stimulation of the gonads or pituitary will rarely be seen by the general practitioner. He must not be influenced by the advertising campaign waged by pharmaceutical houses or by parental anxiety, because the artificial production of puberty has adverse physiological and, especially, psychological consequences on adolescents. Suggestions for conservative therapy with sex and growth hormones are given by the author for each type of case in which it is really needed.

Long-Term Aureomycin Administration in the Prevention of Rheumatic Fever. A. B. Weinstein and C. M. Kurtz. Wisconsin M. J. **54**:423-427 (Sept.) 1955 [Madison, Wis.].

Chlortetracycline (Aureomycin) in an initial dose of 10.4 mg. per kilogram of body weight was given to 28 children between the ages of 5 and 14 years who were known subjects of rheumatic fever. Duration of treatment varied from 5 to 35 months. There were no recurrences of active rheumatic fever in this group. Of the 223 throat cultures taken, 221 were negative and only 2 were positive for beta hemolytic streptococci. The incidence of side-effects was extremely low.

Immunization Against Diphtheria and Whooping-Cough: Combined v. Separate Inoculations. V. Spiller, J. M. Barnes, L. B. Holt and D. E. Cullington. Brit. M. J. **2**:639-643 (Sept. 10) 1955 [London, England].

Two similar groups of infants were used in a small field trial made for the purpose of ascertaining whether the diphtheria antitoxin responses obtained after a course of combined diphtheria-pertussis prophylactic injections started before the age of 6 months were satisfactory. The trial also provided strictly comparable figures by which the relative efficiencies of three doses of fluid diphtheria toxoid combined with pertussis vaccine and two doses of PTAP (purified diphtheria toxoid precipitated by aluminum phosphate) could be compared. Healthy babies ranging in age from 2 to 5 months inclusive on the day of the first injection were allotted at random to the separate or combined method groups. Those in the separate group (79) received three injections each of 1 ml. of suspended whooping-cough vaccine, followed by two injections of 5 ml. of PTAP, all injections being given at monthly intervals. Those in the combined group (81) received three injections each of 1 ml. of combined diphtheria-pertussis prophylactic, also at monthly intervals. All injections were given subcutaneously. The authors used PTAP instead of A. P. T. (alum-precipitated toxoid) because their previous experience showed that it produced fewer and less severe reactions. Blood samples taken from the heel were obtained from each child at the age of 15 months and the serums were assayed for their diphtheria antitoxin and H. pertussis agglutination titers. Three doses of the combined prophylactic gave significantly higher antitoxin titers than those previously reported for two doses of A. P. T. Very young infants inoculated with the combined prophylactic gave higher antitoxin titers than somewhat older ones inoculated with A. P. T. Two doses of PTAP, however, gave the highest figures. The agglutination titers to H. pertussis obtained in the two groups were of the same order, although the whooping-cough vaccines used in them differed in manufacture and H. pertussis content. Present findings give no reason to suppose that a pertussis vaccine combined with fluid diphtheria toxoid is any less effective antigenetically than one given separately. No correlation was found between the responses of individuals to the diphtheria toxoid and the H. pertussis agglutinogen. Children who are still being brought into the investigation are to be followed up clinically for a minimum of two years and the results presented in a later paper.

Immunization of Babies with Diphtheria-Tetanus-Pertussis Prophylactic. M. Barr, A. T. Glenny and N. R. Butler. Brit. M. J. **2**:635-639 (Sept. 10) 1955 [London, England].

Two triple prophylactics, one referred to as adsorbed and one as fluid, were used in immunization trials designed to determine whether satisfactory immunity could be established in very young babies given the first of a course of three injections of the adsorbed preparation at the age of a week and also the optimum age at which to begin immunization with the fluid preparation. Both preparations contained, per milliliter, 60 Lf of purified diphtheria toxoid, 12 Lf of purified tetanus toxoid, and 4×10^{10} H. pertussis; in one, the toxoids were adsorbed on to aluminium hydroxide and in the other no mineral carrier was used. The dose injected into the babies was in all cases 0.5 ml. The question of age at the time of the first dose is of special importance, because the immunization in most babies should be started at a time when the maternally conferred diphtheria antitoxin has fallen below the level at which it will interfere with the action of the diphtheria toxoid in the prophylactic. Most of the babies in this study were born during 1953 and 1954. They were divided into four groups, S, T, V, and Y. Those in group S received three injections of adsorbed prophylactic at the ages of 1, 6, and 14 weeks respectively. Groups T, V, and Y received injections of fluid prophylactic at the following ages: T, 6, 12, and 18 weeks; V, 12, 16, and 20 weeks; and Y, 16, 20, and 24 weeks. A reinforcing dose of the fluid preparation was given to all groups at the age of 52 weeks. Titration for the antitoxin in blood samples taken at various intervals showed that when injections of the fluid preparation were given four weeks apart, starting at the age of 12 or 16 weeks, only one baby in 330 had a diphtheria titer below that usually regarded as the Schick level when tested eight weeks after the third injection. Over 93% had titers at least 10 times this level, and over 75% had titers above 0.2 unit. Not one of the 240 babies tested at the age of 12 months was below the Schick level, and 90% had titers at least 10 times this level. Results were less satisfactory in the group receiving the first injection of the fluid preparation at the age of 6 weeks. The adsorbed triple prophylactic, started when the babies were one week old, caused severe reactions, and, although the diphtheria titers were satisfactory at the age of 6 months, they fell rapidly during the next six months. The tetanus antitoxin titers of all babies were above 0.1 unit per milliliter each time samples were taken, and in 95% of 460 tested at the age of 6 months they were at least 1 unit per milliliter. A rough correlation was found between the diphtheria and tetanus responses in all the groups.

Evaluation of the Results of Penicillin Therapy of Congenital Syphilis in Children. L. Dembińska-Widy. Pediat. polska **30**:553-557 (July) 1955 (In Polish with Russian and English summaries) [Warsaw, Poland].

Five years' experience with 118 infants and children with congenital syphilis treated in the pediatric clinic of the Medical Academy in Poznan, Poland, prompted the following suggestions. In premature babies and infants less than 2 months old with severe lesions, preparatory treatment should be instituted, in order to avoid a Herxheimer reaction. This treatment should consist of acetarsone (acetylamino-hydroxyphenyl-arsonic acid), starting with half of a 0.25 gm. tablet a day and continued for two weeks. Penicillin therapy is instituted after this period. Congenital syphilis should be treated during the first year of life with two courses of penicillin therapy and one of arsenic and bismuth. No changes in the nervous system and no mental disturbance were noted by the author in the infants so treated. In the second year of life one course of penicillin therapy is advised, with three arsenic-bismuth treatments, and, in the third year, one of penicillin and four of arsenic and bismuth. If serologic resistance or serologic recurrence be encountered, as many as six courses may be used. In older children with late congenital syphilis, a too energetic treatment with penicillin or arsenic compounds may cause a Herxheimer reaction. Patients should not be discharged from observation before examination of the

cerebrospinal fluid and auxiliary examinations are performed. After cessation of therapy, children should be examined periodically for three or more years.

Difficulties in Diagnosis of Thyroid Hypofunction in Children. J. Kosowicz and A. Graczykowska. Pediat. polska **30:**543-551 (July) 1955 (In Polish with Russian and English summaries) [Warsaw, Poland].

The diagnosis of thyroid gland insufficiency in children is difficult, because the first symptoms of the disease are not very characteristic and are noted late. The commonest wrong diagnoses for hypothyroidism are rickets and mental deficiency. False diagnoses of primary thyroid insufficiency are made in cases in which the insufficiency is actually secondary to disorder of the central nervous system, or hypothalamohypophysial system, and consequently, requires different therapy. In differentiating hypothyroidism from other diseases, the entire clinical picture should be taken into consideration. Radiological examination of the bones is an aid in diagnosis, since a characteristic sign of hypothyroidism is marked inhibition of the bone age (late appearance of ossification nuclei) that can be seen in the roentgenograms before inhibition of normal growth is noticed in the child. A definite increase in the serum cholesterol level suggests thyroid insufficiency and can therefore be used in the differential diagnosis from mental retardation. Finally, the therapeutic test is of value, especially in the abortive forms of hypothyroidism; improvement after thyroid replacement therapy proves the diagnosis.

UROLOGY

Malignant Lymphomatosis of the Kidneys. R. A. Wentzell and S. W. Berkheiser. J. Urol. **74:**177-185 (Aug.) 1955 [Baltimore].

In 1,047 autopsies performed between 1949 and 1954 at the Robert Packer Hospital in Sayre, Pa., there were 32 cases of histologically proved malignant lymphoma, an incidence of 3%. By reviewing the clinical records, autopsy protocols, and microscopic sections of these cases, renal involvement was found in 17 (53%). Men predominated in a ratio of 8 to 1. All patients were over 50 years of age at the time of death except for six who were between the ages of 11 and 38 years. The kidneys were involved less often in reticulum cell sarcoma (16%) and Hodgkin's granuloma (20%) than in other types of lymphoma, such as lymphosarcoma, Hodgkin's sarcoma, and multiple myeloma, and in leukemia, in which renal involvement was present in 50 to 100% of cases. Primary renal lymphomatosis has never been proved. Any patient with slowly progressive renal failure not easily explained should be suspected of having lymphomatosis involving the kidneys or ureters. Common symptoms and signs are generalized weakness, anorexia, loss of weight, and anemia. Purpura may be present due to thrombocytopenia. Localizing symptoms may direct the physician's attention to the chest or abdomen depending on whether the mediastinal or retroperitoneal lymphoid tissue is the site of the chief lesions. Venous thrombosis and edema of the lower extremities may occur; it is caused by obstruction of veins and lymphatics by retroperitoneal masses. Four of the 17 patients with renal involvement died in uremia. Autopsy revealed bilateral ureteral obstruction by retroperitoneal masses resulting in uremia in two, one of whom had lymphosarcoma and the other Hodgkin's granuloma. Another with chronic myelogenous leukemia and a moderate amount of retroperitoneal enlargement had bilateral hydronephrosis and hydroureters, moderate obstruction of the neck of the bladder caused by benign prostatic hyperplasia, and terminal bilateral pyelonephritis. The fourth patient had multiple myeloma and died of renal insufficiency; dense infiltration of intestinal tissues by plasma cells, lymphocytes, and multinuclear giant cells and obstruction of the renal tubules by protein casts resulted in glomerular and tubular degeneration and atrophy. In all types of lymphoma the patient's life was apparently prolonged and made more comfortable by irradiation or chemotherapy with nitrogen mustard and triethylene melamine.

Further Experience with Transrectal Biopsy of the Prostate. H. Grabstald. J. Urol. **74:**211-221 (Aug.) 1955 [Baltimore].

Transrectal biopsy was made in over 100 patients with suspected carcinoma of the prostate. After thorough cleansing enemas and sterilization of the intestine, preliminary sphincter dilatation was performed with the aid of low spinal or saddle block anesthesia. The Fansler operating rectal speculum was introduced; it permitted easy palpation of the prostate and through it biopsy forceps was easily admitted. A 4 by 8 in. gauze packed in the rectum above the prostate served to stretch the rectal mucosa over the desired biopsy site. A vertical stab incision was made over the suspicious area and the prostate was palpated through the proctotomy, which was easily dilated with the index finger and biopsy forceps together. With the use of sharp-edged forceps, a separate prostatic incision was not necessary. To avoid entering the urinary tract, the bladder must be emptied before surgery; an indwelling urethral catheter may occasionally serve as a midline landmark. The stab incision into the prostate should be directed laterally, toward either lateral lobe, and away from the midline of the prostatic urethra. Of 50 consecutive patients who were subjected to this procedure, a pathological diagnosis of carcinoma was made in 21, chronic prostatitis in 21, benign prostatic hyperplasia in 6, squamous metaplasia without infection in one, and calcinosis with foreign body reaction in one. Thus over 50% of clinically hard or suspicious prostates proved to be benign, while carcinoma was revealed in only 41.1%. Transrectal biopsy is especially useful for the diagnosis of inoperable prostatic carcinoma. The nature of the approach lends itself to ready access to the posterior lamella. A pathological diagnosis of potentially curable carcinoma of the prostate was made in 11 patients. Radical retropubic prostatectomy was carried out in eight and radical perineal prostatectomy in three, thus adding to the evidence that diagnosis of early carcinoma is not so rare as previously believed. Only moderate additional dissection difficulty at the time of radical surgery resulted from the previous transrectal biopsy in most of these patients. A waiting period of three to four weeks between biopsy and definitive radical surgery may be indicated. Earlier intervention before scar formation has certain advantages. There were few complications of transrectal biopsy. Hemorrhage and infection were neither common nor serious. Prostatitis was the most serious inflammatory complication. Fistulas did not occur after transrectal biopsy. Hematuria was rare and was easily controlled by catheter drainage. For most urologists not trained in perineal surgery, radical retropubic prostatectomy combined with a satisfactory preoperative biopsy technique may be the procedure of choice.

Unilateral Renal Purpura: Report of a Case with Clot Formation Simulating Tumor. J. Zellermayer and H. Passman. J. Urol. **74:**191-196 (Aug.) 1955 [Baltimore].

A case of unilateral renal purpura is described in a 25-year-old man who was admitted to the Menorah Medical Center in Kansas City, Mo., with gross hematuria of several hours' duration. He had no other urinary symptoms, no pain, no dysuria, no frequency, and no chills or fever. Excretory urography revealed an irregular filling defect in the pelvis of the right kidney. Gross hematuria persisted for nine days. A right nephrectomy was performed. The postoperative course was uneventful, the urine cleared up completely, and the patient was dismissed on the 11th postoperative day. He remained asymptomatic and well. Microscopic examination of the removed right kidney revealed striking changes in the pelvis and, to a lesser extent, in the peripelvic fat; they consisted of recent hemorrhages, heavy inflammatory infiltration with lymphocytes and eosinophils, and edema, affecting all the major and minor calices. An abundance of small blood clot fragments was observed lying free in calices and pelvis. There were inflammatory foci in the peripheral part of the wall of the ureter and periureteral tissues, essentially similar to those in the pelvis. Lymphocytes were the predominant cells and eosinophils were less abundant in the ureter. Suggestive local fibrinoid degeneration was present in the peripheral portion of the wall of the blood vessels and in the perivascular tissues. The

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heavy eosinophilic leukocytic infiltration in the renal pelvis and peripelvic tissue, the fibrinoid degeneration in the walls of the vessels, and the reaction in the ureter were suggestive of hypersensitivity. Nine similar cases were collected from the literature.

Pressor Gland in Urologic Hypertension. C. Jiménez Díaz and M. Morales Pleguezuelo. Rev. clín. españ. **57:**342-350 (June 30) 1955 (In Spanish) [Madrid, Spain].

The authors report a histological study of the kidneys of five patients with acute hypertension. The kidneys were removed at operation in four patients with unilateral nephropathy and at necropsy of a patient with acute renal disease who died in uremia. The removal of the pathological kidney in the four patients resulted in complete suppression of hypertension. In all five cases the changes of the pathological kidneys consisted of destruction of the glomeruli, atrophy of the tubules, and an enormous hyperplasia and thickening of the walls of the small arteries and arterioles. The lumen of the vessels was almost occluded. The intima was the seat of a reaction of a metachromatic substance like that normally observed in a very small degree in the walls of the arteries for controlling the balance of the blood pressure. The authors believe that the kidney secrets and utilizes or destroys pressor substances in response to the demands of regulation of blood pressure. The pressor substance is a metachromatic substance that is produced during a reaction of hyperfunction of the arterial wall. The tubules are concerned in modifying and using the pressor substance or in destroying it, according to the demands for the regulation of the blood pressure. The lack of destructive power of the tubules upon the pressor substance is the cause of hypertension. As the pressor substance from the kidney passes unmodified into circulation, it elicits a diffuse reaction of hypersecretion of pressor substance from the arterial walls of the entire arterial system.

OPHTHALMOLOGY

Hyaluronidase in the Treatment of Exophthalmic Ophthalmoplegia. L. P. E. Laurent and J. W Scopes. Lancet **2:**537-538 (Sept. 10) 1955 [London, England].

Laurent and Scopes present the history of a 53-year-old man, who was hospitalized because of thyrotoxicosis. He was treated by rest in bed, methylthiouracil, and later thyroid extract. After three weeks his symptoms had disappeared and he had gained 10 lb. (4.5 kg.), but the staring eyes persisted. The treatment with methylthiouracil and thyroid extract was continued after discharge from the hospital. He was seen as an outpatient at intervals of three weeks, and his toxic symptoms and signs remained well controlled, and the dose of methylthiouracil was reduced successively. The exophthalmos steadily increased; edema of the conjunctiva, first noticed in April, was considerable by July; and his eyes were continuously sore and watering. Radiotherapy to the orbit was tried but had to be discontinued. Slight improvement resulted from the application of cold compresses to the eyes. Then hyaluronidase, in the form of Hyalase, was injected into the conjunctiva a few minutes after 2% Decicaine drops had been instilled. During the next two weeks, six such injections were given into the conjunctiva of the worse eye, the right, the left serving as a control. Within 24 hours of the first injection, there was a distinct lessening of the edema, and with each subsequent injection the improvement increased. The left eye meanwhile was being treated with cortisone ointment and was improving, but not so rapidly as that treated with Hyalase. Later, six injections were given into the conjunctiva of the left eye, the application of cortisone ointment being discontinued. The improvement again was distinct and persistent. The next stage was the injection of Hyalase into the orbit itself. There was a clinical impression of improvement in the movements of the eyes, but no measurement of change was possible. The attention of the authors was called to an earlier report by Lebensohn in which it was suggested that hyaluronidase might be useful in thyrotropic exophthalmos.

Retrolental Fibroplasia: Relation to Oxygen Therapy. P. Brændstrup and E. W. Flensborg. Ugesk. læger **117:**1015-1022 (Aug. 11) 1955 (In Danish) [Copenhagen, Denmark].

Systematic examination of 228 premature infants treated in a Copenhagen pediatric department from 1950 through 1954 revealed retrolental fibroplasia in 31 infants, of whom 6 have become blind, 2 have reduced vision, and 7 have permanent changes without functional significance; in 16 the condition was reversible. Slight irreversible changes occurred after five days' treatment with oxygen; permanent retinal degeneration reducing vision was not demonstrable till after two weeks' treatment. Since 1952, oxygen therapy for premature infants has been given only on urgent indication and then as little and for as short a time as possible. Analysis comparing the frequency of retrolental fibroplasia during the two periods with the different oxygen regimes supports the theory that the affection is induced by oxygen therapy for premature infants. Oxygen treatment of premature infants should be avoided whenever possible and employed only on the strictest indication.

Retrolental Fibroplasia in Nebraska. S. M. Truhlsen. Nebraska M. J. **40:**293-295 (Aug.) 1955 [Lincoln, Neb.].

Of 41 known blind children of preschool age in the state of Nebraska, 20 (49%) are blind because of retrolental fibroplasia. In addition, five children in the School for the Blind at Nebraska City are blind because of this disease. Increasing evidence from many sources indicates that a large majority of these children are blind because too much oxygen was administered routinely during the first few days of life. In accordance with these findings, it is suggested that, after the first 48 hours, oxygen should be restricted entirely or limited to minimal amounts dictated by clinical need and that a maximum oxygen concentration of 40%, as determined by an oximeter, should be given unless special critical conditions supervene. When oxygen is given, the percentage administered should be withdrawn gradually rather than suddenly. In cases of marked visual impairment, it is suggested that the parents of the child be advised to consult the Services for the Blind for help and guidance in the period of adjustment and rehabilitation.

Isoniazid and Ocular Tuberculosis: An Evaluation of Experimental and Clinical Results. W. H. Kratka. A. M. A. Arch. Ophth. **54:**330-344 (Sept.) 1955 [Chicago].

Experiments on rabbits showed that isoniazid has definite bacteriostatic, and possibly bactericidal, effects in milder tuberculous infections in the anterior chamber. The abnormal changes observed in the treated eyes were considerably less than those observed in the nontreated eyes. Definite clinical improvement followed about 21 days of therapy. After 70 days of therapy, all clinical activity had ceased and laboratory studies were negative for tubercle bacilli and showed only low-grade inflammatory activity. Isoniazid was given a therapeutic trial in 94 patients with ocular tuberculosis. The patients received an average of 300 to 400 mg. of the drug per day orally. This was divided into 100 mg. doses given at four to six hour intervals. Isoniazid ointment (200 mg. per gram) was used topically at bedtime in the anterior segment lesions. In most of the patients, no marked changes were noted in the first two to three weeks of therapy, after which improvement was fairly rapid in those patients who did respond. Patients with posterior uveitis and those with periphlebitis and hemorrhage responded best to therapy, 69% being improved. The next best response was noted in patients with anterior uveitis; 52% of these patients were improved. Treatment with isoniazid was continued in all patients for a minimum of four months despite apparent clinical cures within two months in many patients. This prolonged therapy was based on the experimental studies that showed that pathological activity could be present despite a lack of clinical activity. Apparent cures were obtained in 56 of the 94 patients. Recurrence after therapy was observed in only three cases, two of which were sarcoid in origin. Isoniazid has definite value in the treatment of ocular tuberculosis in man. The drug appears to be nontoxic and is easily administered. It is inexpensive and makes frequent office visits or hospitalization unnecessary. Treatment must continue for at least four months to obtain clinical cure.

THERAPEUTICS

Studies on Coronary Blood Flow, with Emphasis on the Treatment of Coronary Insufficiency. W. L. Jamison, L. De Vera, G. Katakis and others. J. Am. Geriatrics Soc. **3:**521-526 (Aug.) 1955 [Baltimore].

Norepinephrine has recently been reported to have a beneficial effect in shock following myocardial infarction. Most clinicians regard this drug as one that elevates blood pressure and thus causes an increase in coronary flow. Data obtained from circulatory studies in mongrel dogs, however, show that it is a potent coronary vasodilator and that it produces an increase in coronary blood flow far exceeding its effect on the blood pressure. Ten of the first experiments in this series dealt with the effect of methoxamine hydrochloride (Vasoxyl) on the blood pressure and coronary blood flow. The observations covered a period of five minutes and were not accompanied by oxygen measurements. The flow decreased slightly at times, but in general the findings suggest that the effect of methoxamine on the coronary blood flow is proportional to the rise in the blood pressure. Norepinephrine, on the other hand, was found in three contrasting experiments to have a much greater effect on the coronary blood flow than on the blood pressure. A similar increase in coronary blood flow was also produced by natural epinephrine, which was used in five other experiments. Experiments in which oxygen consumption studies were made showed that the increase in coronary circulation after the administration of both norepinephrine and epinephrine was greater than that in oxygen utilization by the heart. The coronary venous oxygen content rises because the oxygen supply of the heart muscle is raised to such an extent that the heart muscle no longer needs to take the maximal amount of oxygen out of the coronary blood. This finding was in harmony with the gross observation that the coronary venous blood turned bright red after the administration of norepinephrine and epinephrine, whereas when methoxamine was given it had remained black.

Evaluation of Orally Administered Penicillin. W. P. Boyer. J. Am. Geriatrics Soc. **3:**556-565 (Aug.) 1955 [Baltimore].

Doubts in regard to the reliability of orally administered penicillin rest largely on studies carried out years ago with doses that now seem ridiculously small. The early investigators were compelled by practical considerations to recommend only parenteral administration of what was then a rare and new antibiotic with a potency of only from 40 to 50 units per milligram as compared with 1,670 units per milligram today. A reappraisal of these recommendations, however, is now under way. The increased availability and greater potency of the drug, as well as the many new forms in which it is now being supplied, have started an unmistakable trend toward its oral administration. The Scandinavians, in particular, are ahead of the United States in accepting oral penicillin therapy. The penicillemia (penicillin plasma concentration) demonstrated by investigators using small oral doses (10,000, 20,000, and occasionally 50,000 units) was slight and transient, but now with doses of 100,000 units or more given orally all the author's patients have shown a penicillemia of variable duration. Penicillin has also been recovered in the urine after the administration of smaller oral doses, even when it could not be demonstrated in the plasma, proving that absorption had taken place from the gastrointestinal tract. Repeated studies have shown that the same dose of penicillin administered to the same patients under the same conditions gives rise to a reproducible penicillemia. Variations in the absorption of penicillin from the gastrointestinal tract reflect the physical and pathological differences between patients and should lead to even greater individualization of dosage schedules. Statements about penicillin therapy should always be qualified by reference to the type of penicillin used, the route of administration, and the size of the dose. Orally administered doses of some of the insoluble penicillins (procaine penicillin, benzathine, and benethamine) are capable of producing higher peak concentrations in the plasma than those produced by the same penicillins given parenterally. None of the penicillins presently available, however, has been shown to be superior to potassium or sodium penicillin G in giving a prompt and predictable penicillemia. Objections on the ground of unpalatability can be overcome by suspending the penicillin in anhydrous coconut or peanut oil. The oral administration of 1 million units of sodium or potassium penicillin produces a penicillemia comparable to that resulting from the intramuscular injection of 200,000 units of water-soluble penicillin. Penicillin given orally in reasonable dosage (200,000 units administered three or four times a day) can induce penicillin plasma concentrations greatly in excess of those produced by the intramuscular injection of 10,000 units of potassium penicillin every four hours, which have been shown to be therapeutically effective. The use of probenecid given orally in combination with penicillin results in a twofold to fourfold increase in the resulting penicillin plasma concentration, so that the maintained penicillemias are comparable to those occurring after the parenteral administration of repository penicillins. These findings show that orally administered penicillin is applicable to the therapy of most of the common penicillin-treatable infections.

The Use of Prednisone (Meticorten) in Respiratory Disease: II. Pulmonary Emphysema and Pulmonary Fibrosis. H. A. Bickerman, G. J. Beck and A. L. Barach. J. Chron. Dis. **2:**247-259 (Sept.) 1955 [St. Louis].

Results of administration of prednisone to patients with bronchial asthma were reported by the authors in a previous paper (*J. A. M. A.* **158:**1396 [Aug. 13] 1955). Similar methods of administration of prednisone were used in 50 patients, 12 of whom had extensive pulmonary fibrosis complicated by varying degrees of bronchopulmonary infections; the remaining 38 patients had pulmonary emphysema, which was associated with fibrosis in 7. There were 39 male patients and 11 female patients, all between the ages of 15 and 74. The drug was given in four divided doses daily. The average daily dose of prednisone given was 50 mg. on the first day, 35 mg. for the first week, and 20 mg. (maintenance dose) for 60 days. The results obtained differed from those obtained with cortisone and corticotropin (ACTH) in the following ways. Moderate to marked improvement with relief of dyspnea and increased tolerance occurred in 43 patients (86%) treated with a daily dose of prednisone averaging one-quarter that employed with cortisone. The onset of subjective improvement was significantly more rapid than with cortisone, usually within 48 hours after treatment was instituted. A striking loss of body weight ranging between 3 and 9 lb. (1.3 and 4.1 kg.) occurred in 12 of the 50 patients in the course of the first week of therapy, including patients with cor pulmonale who had not responded favorably to cortisone. A decrease of 8 and 9 lb. (3.6 and 4.1 kg.), respectively, occurred during the first week of treatment with prednisone in two of four patients who had not previously been treated with cortisone. The possible mechanism of this weight loss at a time when appetite and food intake were increased deserves further study. With the exception of salt and water retention and the decreased incidence of moon face or fat deposition, other untoward reactions observed with cortisone were observed likewise with prednisone, especially gastrointestinal disturbances and reactivation of sinobronchial infection. As a precautionary measure, administration of prednisone with milk and the addition of aluminum hydroxide or calcium carbonate two hours after meals and on retiring is advocated. Concurrent administration of the broad spectrum antibiotics such as tetracycline is suggested, particularly in patients with bronchitis or bronchiectasis.

Practical and Theoretical Notes on the Introduction in Therapy of Prednisone (Metacortandracin). L. Villa and C. B. Ballabio. Minerva med. **46:**1-4 (July 4) 1955 (In Italian) [Turin, Italy].

The authors' experience with prednisone (metacortandracin) on more than 70 patients with various conditions indicated that this new steroid is several times more potent as an anti-inflammatory agent than cortisone and that the side-effects are less marked than those occurring after cortisone or corticotropin therapy. In addition, it does not interfere negatively with the water-mineral exchange. Administration of the preparation to 14 patients with rheumatic carditis indicated that it is particularly suited for treatment of this condition. Prednisone gave good results in patients with asthma, scapulohumeral peri-

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arthritis, and gout. It had a diuretic effect on patients with nephrosis in whom diuresis reappeared on the 4th or 5th day of therapy and was completely restored by the 10th day. It benefited three patients with Addison's disease in whom the effects, after the administration of relatively low effective doses (5 to 10 mg. daily), were comparable to those of cortisone. In addition to clinical improvement, a marked fall in the 17-ketosteroid excretion was observed in one patient with the adrenogenital syndrome. In blood diseases, the activity of this steroid was four to five times greater than that of cortisone. From the metabolic standpoint, prednisone does not cause sodium retention, potassium depletion, or hypochloremic alkalemia. Its interference with the carbohydrates' metabolism is not great. Changes in the plasma proteins are like those caused by cortisone, but they can be more severe and occur more frequently if large doses of this steroid are given. A slight moon-shaped face, acne, and hirsutism were some of the side-effects. They indicate the adrenocortical-like nature of prednisone, which, therefore, should be used with caution.

Prednisone in Bronchial Asthma. U. Serafini, A. Pieri and U. Di Nardo. Minerva med. **46:**22-26 (July 4) 1955 (In Italian) [Turin, Italy].

Prednisone administered to 12 patients with bronchial asthma of long standing brought about a partial or total remission of the symptoms in most. The drug was given for from 6 to 18 days in doses of 30 mg. daily for the first two days and of 10 to 15 mg. thereafter. The total dose ranged from 130 to 370 mg. The patients began to improve during the first 24 hours of therapy, and the symptoms subsided within two to three days. The results were excellent, with disappearance of cough and dyspnea, euphoria, increased appetite, and capacity for rest, in seven patients, good in two, and mediocre in two. The remission lasted from a few days to a few weeks or several months. One patient with respiratory insufficiency secondary to marked pulmonary emphysema was not benefited by the therapy. The side-effects were less frequent and less marked than those that usually follow the administration of hormonal steroids to patients with asthma. A slight increase in body weight was noted in three patients, and acne pustulosa and a slight moon-shaped face in one.

Hydrocortisone by the Intrapleural Route in Treatment of Parapneumothorax Pleurisy. C. Sartori. Prog. med. **11:**401-406 (July 15) 1955 (In Italian) [Naples, Italy].

Results following the intrapleural administration of hydrocortisone to 15 patients in whom pleurisy and empyema developed in the course of therapeutic pneumothorax are reported. The hormone, which was introduced into the pleural cavity in an isotonic suspension after the exudate was aspirated, was given every other day or every three to four days in doses ranging from 25 mg., on the first days, to 100 mg. The total dose ranged from 100 to 960 mg. The anti-inflammatory action of hydrocortisone was marked and rapid in serous and serofibrinous pleurisy, less marked in empyema. The therapy restored to normal or to subfebrile values the elevated temperature in all of the patients; it never aggravated the pulmonary disease; and it improved the general condition of all but one patient. Sartori states that in the patients with serofibrinous and exudative pleurisy hydrocortisone acted in a nonspecific manner by eliminating or decreasing the tissue hyperactivity, which is, in most cases, the physiopathogenic basis of pleurisy that develops during the course of therapeutic pneumothorax. The hormone was less efficacious in purulent pleurisy because, in addition to the allergic-hyperergic factor, the tuberculous bacterial factor was also present.

Mestinon: New Agent in Treatment of Myasthenia Gravis. A. Lønnum. Tidsskr. norske lægefor. **75:**581-582 (Aug. 15) 1955 (In Norwegian) [Oslo, Norway].

In the drug treatment of myasthenia gravis, neostigmine and similar substances have long been the best agents. The brief duration of their effect and the frequent side-effects have led to the trial of new substances, among which Mestinon seems to offer many advantages, as observed in seven patients with myasthenia gravis treated with it in the neurological department of the Rikshospital since January, 1955. The maximal effect of Mestinon is not greater than that of neostigmine (Prostigmin), but the by-effects are fewer and less marked. The action of Mestinon is more even, and the patient's well-being is promoted. The agent is most often applied alone, but some patients prefer a combination with neostigmine, which gives the advantage of the rapid effect of neostigmine in addition to the prolonged effect of Mestinon.

PATHOLOGY

Bronchogenic Carcinoma: A Clinicopathologic Study of 75 Fatal Cases. R. S. Armstrong, H. L. Papenfuss and B. C. Russum. Nebraska M. J. **40:**315-323 (Sept.) 1955 [Lincoln, Neb.].

The possible relationship of histological type, growth characteristics, and site of tumor origin to prognosis was studied in 60 men and 15 women who died of bronchogenic carcinoma, in whom autopsies were performed and for whom satisfactory clinical records were available. Of the 15 women, 8 had adenocarcinoma, one undifferentiated carcinoma, 5 squamous cell carcinoma, and the histological type was unknown in one. Of the 60 men, 14 had adenocarcinoma, 21 undifferentiated carcinoma, 22 squamous cell carcinoma, one alveolar carcinoma, and the histological type was unknown in 2. Adenocarcinoma thus was observed relatively twice as often in women as in men, and the incidence of squamous cell carcinoma was approximately the same in each sex. Of the 75 tumors, 22 were adenocarcinomas, a higher proportion than usually reported, probably because of the greater number of women in the series. Adenocarcinomas were more rapidly growing, peripherally infiltrating tumors with frequent vascular invasion and metastases; death usually occurred within eight months after symptoms appeared. Squamous cell carcinomas were most commonly relatively circumscribed and grew and extended slowly to produce bronchial obstruction; duration of life from onset of symptoms to death of patients with this type of carcinoma was the longest of the entire series. Undifferentiated carcinomas were even more rapidly growing than the adenocarcinomas; they were centrally infiltrating tumors, producing bronchial obstruction and causing death in 6.9 months. The dominant pathological findings in all cases were bronchial obstruction with peripheral atelectasis or pulmonary inflammation, extensive invasion of extrapulmonary tissues, as well as numerous and diverse metastases. The usual clinical picture suggesting bronchogenic carcinoma consists of cough, dyspnea, and chest pain in a middle-aged white man with associated physical findings of minimal chest signs, anemia, leukocytosis, and a chest roentgenogram with nonspecific changes. The varieties of clinical pictures resulting from the characteristic development of the neoplasm, such as recurrent pneumonia produced by bronchial obstruction, predominant extrapulmonary symptoms caused by metastases, and the value of roentgenograms of bones, are stressed. The findings in the authors' 75 cases suggest that the clinicopathological picture becomes similar for all histological types as the bronchogenic carcinoma progresses. Autopsy findings in patients dying of bronchogenic carcinoma provide excellent background for understanding the pathogenesis of the established advanced disease and aid in diagnosis and palliative therapy, but they fail to furnish the best criteria for early diagnosis. Such criteria must be obtained from analysis of a large series of very early tumors detected by biopsy or removed surgically, or observed incidentally at autopsy.

Cystinosis (Lignac-Fanconi Disease). C. D. Gatzimos, D. M. Schulz and R. L. Newnum. Am. J. Path. **31:**791-808 (Sept.-Oct.) 1955 [Ann Arbor, Mich.].

Cystinosis is an uncommon disease of infants and children characterized by retarded development, dwarfism, storage of cystine crystals in the cells of the reticuloendothelial system,

and aminoaciduria. Rickets is usually present. Since Lignac's classical description of the disease in 1924, it has been known under such terms as cystine storage disease, cystinosis, and Lignac's disease. It is also known as Lignac-Fanconi disease. The authors briefly mention five cases of this disease, which were reported in the American literature in the three years from 1950 to 1952, inclusive, and describe a case observed by them, which concerned a 33-month-old girl who was hospitalized because of dehydration and acidosis. The child died shortly after the physical examination. In describing the postmortem examination, the authors stress the presence of cystine crystals in the mesenteric lymph nodes; in the reticuloendothelial cells of the spleen; in the liver between the hepatic cords, primarily near the central region of the lobules, throughout the bone marrow, but especially adjacent to the trabeculae; in the medulla of the thymus; in the submucosal lymphoid follicles of the intestine; in the stroma of the choroid plexus; and in the interstitial tissues of the pancreas, thyroid gland, adrenal capsule, lung, and the mucosa of the ileum. Rickets and dwarfism were present. Renal changes consisted of glomerular sclerosis, interstitial fibrosis, arteriolar sclerosis, and hydropic degeneration of the tubular epithelium. Cystine, isolated from mesenteric lymph nodes, was identified by several chemical tests. In retrospect, the clinical features in the present case were rather typical and the diagnosis was suspected while one of the authors was treating the child for recurrent episodes of fever with respiratory infections. Once suspected, the diagnosis may be established by finding cystine deposits in the cornea by use of the slit lamp. Biopsy of the conjunctiva may reveal cystine crystals. When photophobia is present, dystrophic changes may be detected in the corneal epithelium with the aid of fluorescein. Bone marrow aspiration will reveal typical crystals, particularly in stained films. Urine studies by paper partition chromatography reveal aminoaciduria. The degree of renal involvement is variable.

INDUSTRIAL MEDICINE

Disabling Pneumoconiosis from Limestone Dust. A. T. Doig. Brit. J. Indust. Med. **12:**206-216 (July) 1955 [London, England].

Limestones are extensively employed in agriculture; in the building and allied trades; in the chemical and metal industries; in coal mines; in the manufacture of paints, paper, glass, soap, pottery, pharmaceutical preparations, and explosives; in the textile and printing trades; in railway engineering; in furnace construction; and in polishing of metals. Although limestone dust is generally regarded as harmless, the author reports observations on eight limestone workers in whom pneumonoconiosis developed. Five of the patients were grinders of limestone and three were miners. The mean duration of employment that involved exposure to dust of limestone was 26.1 years. Three of the eight men with pneumonoconiosis had no history of exposure to any industrial dust other than limestone, and, in one other, such exposure amounted only to six months as a whinstone quarryman. In all the remaining cases the exposure of the patient to limestone was considerably in excess of exposures to other dusts. Three of the limestone grinders had no obvious disability; of the remaining five pneumonoconiosis patients, three were partially disabled, one was totally disabled, and one had died of the disease. Symptoms were slight or absent in those who were not disabled; in the others dyspnea was the most prominent symptom and cough and sputum were present. X-ray findings were variable; large, massive shadows were present in the fatal case, nodulation in three, reticulonodulation in two, and reticulation with diminished translucency and fluffy shadows in the remaining two cases. Postmortem examination in the fatal case showed extensive nodular fibrosis of the lungs. The noxious constituent of the limestone can only be the calcium carbonate, the free silica, the combined silica or silicates, or one of the other constituents. Some are of the opinion that calcium carbonate dust has a beneficial action on quartz, decreasing its toxicity. The occurrence of these cases of silicosis as a result of exposure to dust containing between 1.8 and 12.1% of free silica and 85 to 95% of calcium carbonate would not appear to indicate any inhibitory effect of the latter material. The pneumonoconiosis hazard in the mining and grinding of at least certain limestones is considerable in spite of the relatively low free-silica content.

Cutting Oils and Squamous-Cell Carcinoma: Part I: Incidence in a Plant with a Report of Six Cases, E. Mastromatteo; **Part II: An Experimental Study of the Carcinogenicity of Two Types of Cutting Oils.** J. P. W. Gilman and S. D. Vesselinovitch. Brit. J. Indust. Med. **12:**240-243 and **12:**244-248 (July) 1955 [London, England].

The occurrence of skin cancer in machine operators is of interest because of its possible relation to exposure to petroleum products, chiefly the cutting oils. The author presents the histories of six patients with squamous-cell carcinoma of the skin and of one patient with papilloma of the skin. The men were employed in a single plant in which various types of machines were used. The time of exposure in five of the cases ranged from 13 to 31 years, with an average of 21 years. The exposed skin of the hand and forearm was involved in all cases except one, in which the scrotum was involved. Three of the patients with carcinoma and the patient with papilloma did most of their work on automatic machines. Two of the cutting oils in use were tested experimentally for their carcinogenic effect. One of these oils was a soluble cutting fluid in the form of a stable oil-in-water emulsion containing active additives, about 45% sulfurized mineral oil base, and 40% water when marketed. It is usually diluted with eight or more parts of water before use. The other oil is a straight cutting oil, a sulfurized mineral oil blended with fatty oils. It is usually cut back with a low viscosity straight paraffin oil before use. The first type of soluble cutting fluid proved to be carcinogenic to three different strains of mice. The response of test groups to a standard skin painting technique varied with the strain used from 19 to 61% tumors after 310 days' exposure. Results proved reproducible and comparatively constant in two trials repeated after an interval of 18 months. The responses in mice to 1:4 and 1:8 aqueous dilutions of this soluble oil were compared with the undiluted product and with a 1:8 used dilution after 365 days' exposure. A marked reduction in the percentage of mice bearing tumors and an increase in induction periods accompanied dilution. Evidence suggests that the chief effect of dilution is the lengthening of the induction period. Results of tests using a straight cutting oil (blend) suggested that this type may also be carcinogenic to the mouse.

RADIOLOGY

Cancer of the Thyroid Gland: Our Experience with Radioactive Iodine. P. E. Russo and H. H. Mathews. South. M. J. **48:**937-940 (Sept.) 1955 [Birmingham, Ala.].

Thirteen patients with cancer of the thyroid treated by I^{131} reacted in one of three different ways: two had high uptake on the part of the tumor, with resultant subjective and objective improvement; four had little uptake but experienced some temporary improvement without marked alteration of the course of their disease; and seven had no uptake and no favorable response to therapy. Most of the patients had had previous surgical and radiation treatment. Six patients of the series are now dead, three of them not having survived over 18 months. Of the seven living, all but one have evidence of existing disease, but there are some in this group who have survived as long as 21 and 26 years with their disease. Surgery, with or without external irradiation, still remains the treatment of choice for the great majority of thyroid carcinomas. A small percentage of these tumors, probably about 15%, will have an avidity for radioiodine, in which case this form of treatment gives excellent results. In patients in whom neither further surgical nor external irradiation therapy is indicated, I^{131} should be administered in an attempt at palliation.

BOOK REVIEWS

Anxiety and Stress: An Interdisciplinary Study of a Life Situation. By Harold Basowitz, Ph.D., Harold Presky, Ph.D., Sheldon J. Korchin, Ph.D., and Roy R. Grinker, M.D. Cloth. $8. Pp. 320, with 44 illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E.C.4, England, 1955.

Much of the research on the relationship of stress to anxiety has been conducted either under highly artificial laboratory conditions or with chronically anxious patients. The study of normal persons reacting to the stresses of real life situations has been largely neglected. To remedy this defect the authors went to the airborne training center at Fort Benning, Ga. There they found a population of young men in superb physical condition who showed few manifestations of psychiatric disease. The three week paratroop training program provided a standard situation of physical and emotional stress. The experimenters found it relatively easy to integrate their procedures into the rigid training schedules. This monograph is a report of the psychological and biochemical changes that they observed in a group of soldiers undergoing paratroop training. The book begins with a chapter in which anxiety and stress are defined. The authors emphasize that anxiety is a feeling state that functions adaptively as a signal of impending danger. When this state exceeds certain limits of intensity, anxiety can become a cause of disordered or maladaptive behavior. Since it is a feeling state, anxiety proper can be studied by psychological techniques only. It is complexly interrelated, however, with social, physiological, neurological, and biochemical concomitants, each of which require special methods of study. This chapter is followed by a brief review of recent researches relevant to the authors' study. The remaining chapters take up in detail problems of experimental design, the data they collected, and their analysis of these data. A large number of figures, tables, and summaries help the reader to follow their argument.

Although many of their conclusions are preliminary, several facts stand out. The experimenters found that the paratroop training program was not as stressful for the candidates as they thought it would be, and as a result the induced psychological and biochemical changes were not as extensive as anticipated. They found that fear of failure was a more potent source of stress than fear of painful injury. They confirmed the fact that eosinopenia develops in response to stress. Although an increase in hippuric acid secretion in response to stress that the authors anticipated on the basis of previous work did not occur, those who excreted high levels of hippuric acid initially showed greater psychological and biochemical reactivity to stress than those who did not. They demonstrated an impairment in digit memory and perceptual discrimination in response to stress. Unexpectedly, the authors encountered the most striking evidences of anxiety after the period of training was over, a fact that they referred to as the end phenomenon. Of greater significance than the findings obtained or their interpretation is the fact that the authors achieved their main object, which was to set up a group of conditions permitting the study of anxiety as it develops in a real life situation. They believe that they have laid the groundwork for an extensive investigative program. This monograph may be studied with profit as a contribution to the problem of experimental design by all who are interested in psychosomatic research.

Human Physiology. By F. R. Winton, M.D., D.Sc., Professor of Pharmacology, University College, London, and L. E. Bayliss, Ph.D. Fourth edition. Cloth. $8. Pp. 616, with 236 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6; J. & A. Churchill, Ltd., 104 Gloucester Pl., Portman Sq., London, W.1, England, 1955.

As in the third edition, Drs. Winton and Bayliss are essentially editors rather than authors of this book. In 13 of the 17 chapters, 15 scientists are listed as the authors. This book is primarily written for medical students. The planned brevity of the book is due to the editors' belief that our medical students are expected to learn too much and to think too little, but we must insist that brief but factual outlines of the steps in research that have lead to our present knowledge of the machinery of the human body in health and in disease are stimuli to thinking on the part of our students. The brevity of the book is achieved by elimination of much of this type of data. Does this stimulate our students to think? An able teacher can make up for these shortcomings. The editors state that, in this edition, "Much of the older wood has been drastically pruned, providing space for new shoots. Nine chapters have been largely rewritten." The presentation is usually precise, factual, and up-to-date, but loose thinking and expression may slip in, even in an essentially good book. On page 2 we read: "Perhaps the most characteristic feature of health is that a man can move about as quickly and for as long [a] time as he likes." This is not true. Competing athletes will testify to the contrary, and even a healthy man, trying to run from the charging tiger, is lacking not in will but in speed.

Neurochemistry: The Chemical Dynamics of Brain and Nerve. Edited by K. A. C. Elliott, Irvine H. Page, and J. H. Quastel. Cloth. $19.50. Pp. 900, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1955.

This monumental symposium by 32 leading biochemists, physiologists, and neurologists from the United States, Canada, Great Britain, and Sweden constitutes a review of present knowledge of the chemistry of the nervous system. As stated by the editors, such a book cannot be fully comprehensive. Nevertheless, its range is wide. Beginning with a dedicatory biographical sketch of J. L. W. Thudichum (1828-1901), who is described as the father of brain chemistry, it covers the chemical constituents of the nervous system, the basic chemical and metabolic changes underlying neurological function, and such fundamental physiological processes as tissue respiration, circulation of blood and spinal fluid, transmission of the nerve impulse, the exchange of electrolytes, and the wide-ranging actions of acetylcholine, cholinesterase, arterenol, and the steroid hormones. The chemistry of pathological states is also dealt with extensively, including the effects of neurotropic drugs, bacterial toxins, and snake venoms as well as the toxic effects of oxygen. The biochemistry of narcosis, of the convulsive states, and of demyelination are discussed. Although chiefly biochemical in orientation, the book presents some of the clinical aspects of neuromuscular and nutritional disorders of the nervous system, discussions of blood analysis in behavioral disturbances, and such metabolic errors as those found in phenylketonuria and the lipoidoses. Comparative neurochemistry receives attention in a chapter on the nervous system of arthropods, and the volume closes with a short suggestive discussion of the thermodynamics of the message by the mathematician, Norbert Wiener.

It would be difficult to overestimate the importance and value of this authoritative book in which the whole field of neurochemistry is surveyed. (Thudichum's book, appearing in 1884, was an important pioneer contribution, while the only recent similar work, by Page, a present editor, was published in 1937.) For the physiologist and biochemist, it presents a review of the current situation in neurochemistry. For the physician, and especially for the neurologist, it serves as a reference book to which he can go for an introduction to a highly technical field largely unfamiliar to him. For further details extensive bibliographies are given. Certain facts become obvious on reading this book. Despite the vast effort expended and knowledge gained, the deficiencies of our information in many areas are easily apparent. Much is now known about the transmission of the nerve impulse, but nothing about the chemical basis, if it exists, for the specificities of sensory modalities, for inhibition, or for the details of convulsive phenomena. In many areas clinical data far surpass chemi-

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

cal explanation. For example, descriptions of the action of neurotropic drugs by Toman, of bacterial toxins by Stevenson, and of snake venoms by Braganca are clinically full, but the chemical events underlying them are largely unknown. Again, although the editors state, "The ultimate objective of Neurochemistry . . . is the understanding of the phenomena underlying the behavior of nerve, brain and mind," it is abundantly clear that our knowledge is far too fragmentary and discontinuous to make the objective more than a fervent hope.

Contradictions reflect differences of opinion, as is inevitable in any symposium. Debate waxes hot over the roles of acetylcholine and cholinesterase in neuronal function. For example, Nachmanson writes (page 402), "The role of acetylcholine in conduction is both general and essential," while Gerard dissents. "The total body of evidence . . . seems unequivocal in excluding acetylcholine from a significant role in the conduction process proper." Such contradictions are well bridged over in the splendid chapter on the physiological significance of acetylcholine by Burgen and MacIntosh. Their article passes fair and balanced judgment on disputed points and constitutes a valuable reference work for both biochemist and clinician. This epochal book mirrors faithfully the present status of neurochemistry, both as to what is known and as to what theories are disputed and accepted, and it leaves the thoughtful reader with a keen realization that much remains to be done. The index is adequate, the typography and format attractive, and the binding sturdy, as befits a book destined to serve in the laboratory.

A Doctor's Book of Hours Including Some Dimensions of the Emotions. By Merrill Moore. Cloth. $6. Pp. 397. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, Canada, 1955.

The author of this book of sonnets is a physician practicing psychiatry, both in private practice and at the clinic. He has traveled afar and has been to war in China and in the Pacific Islands. His observations on people and the things he encounters seem to flow as sonnets from his mind as easily and gracefully as water from a bubbling spring. His poetry is arranged in this book in 12 chapters entitled "Analysis of Men," "Analysis of Women," "Natural History," "Libido," "The Clinic," "The Poet Speaks," "Travel," "War and Violence," "Public Affairs," "City Life," "At the End," and "Philosophic." How so many of his thoughts come to be expressed in poetic form seems to be explained in the following sonnet:

> Occasionally I feel an inward need
> To take a pen and let my feelings bleed
> Through its ink on paper as blood might
> Onto grass, the finish of a fight.
>
> Sometimes a constellation in the sky
> Moves me so; or the Pleiades wheel by;
> And I am touched in ways I cannot say
> By the movement of the lights across the bay.
>
> Sometimes travel, sometimes being alone
> Seems to cut my feelings to the bone.
>
> Sometimes Pullman cars, an upper berth,
> The movement of the winds above the earth
> Touch and tease me, will not let me go
> Until my pulse, then fast, returns to slow.

Clinical Pathologic Conferences of Cook County Hospital. Volume I: Cardiovascular-Renal Problems. Edited by Hans Popper, M.D., Ph.D., Director, Department of Pathology, Cook County Hospital, Chicago, and Daniel S. Kushner, M.D., Associate Director of Medical Education, Cook County Hospital. Cloth. $5. Pp. 325, with illustrations. Blakiston Division, McGraw-Hill Book Company, Inc., 330 West 42nd St., New York 36, 1954.

One of the striking phenomena of medicine in the 20th century has been the development of new methods for keeping practitioners up-to-date on professional problems and advances. As the editors point out in an interesting historical introduction, clinicopathological conferences, first introduced in simple form by the late Richard Cabot of Boston as a method of teaching medical students, are now commonly used in most American and many European hospitals as one means of interesting and informing their staffs and postgraduate students. The 52 discussants in the present volume are members of the staff of the Cook County Hospital, except for an occasional distinguished visitor. After presentation of the clinical history and physical and technical findings in each patient, diagnostic possibilities are freely canvassed by physicians unacquainted with the pathological findings. The last are then presented, usually by Dr. Hans Popper, with questions and discussion by other members of the group. The book is the first of a series planned to cover different types of disease. A brief index lists final pathological diagnoses under three types of problems, cardiac, vascular, and renal. The work, attractively bound in green cloth, is printed on substantial paper in clear, legible type. The many plates, mostly photographic reproductions of roentgenograms or of gross or microscopic preparations, are well reproduced. The discussion of each case is followed by a brief bibliography referring to the outstanding lesions found. The text, which has been carefully reviewed by the discussants and editors, is clear and understandable. The book presents an interesting and instructive discussion of cardiovascular-renal diseases and their complications, many of the cases being quite unusual. It is worthy of careful perusal.

Gynecology: Surgical Techniques. Compiled and edited by Robert J. Lowrie, M.A., M.D., F.A.C.S., Associate Clinical Professor of Obstetrics and Gynecology, College of Medicine, New York University, New York. Foreword by J. P. Greenhill, M.D. Cloth. $17.75. Pp. 552, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto, 2B, Canada, 1955.

This is the companion volume to "Gynecology: Diseases and Minor Surgery," which came out about three years ago. That volume, like this one, was a compilation of articles by many authors and was very well received. Here we have 59 contributors who are truly specialists within a specialty. Although varying techniques are presented by contributors who differ somewhat in their approach, a surprising unanimity is apparent throughout the book. The surgeon who does not regard himself as perfect in his technique or skill should find just what he needs in these pages; the experienced surgeon who is still open-minded to the work of others should be glad to try out other methods described in this book in order to broaden his outlook and to compare the final results. Here we have basic techniques in both major and minor pelvic surgery. The many subheads are printed in bold face, which facilitates reference. In his preface, Dr. Lowrie exhibits a sly sense of humor when he speaks of "the sacred ground of the female pelvis" to be trod by the general surgeon, but "not always with the full blessing of the gynecologist." The compiler has written the first chapter, which deals with the general principles of operative gynecology. The subheads are: Immediate Preparation for Operation; Briefing the Surgeon; Responsibility of the Surgeon; Anesthesia (choice and types of); Supportive Measures; Equipment and Assistance; Extent and Duration of the Operation; The Incision; Adhesions; Closure of the Abdomen; Reoperation; Pregnancy Discovered or Suspected at Laparotomy. The last is of special importance because the surgeon who has failed to diagnose pregnancy will have a hard time explaining his findings after opening the abdomen. It seems trite to insist on a careful, detailed, and exhaustive history, but that must be stressed repeatedly. With few exceptions, the transperitoneal approach in cesarean section would seem preferable to the extraperitoneal because it is simpler and, as some would probably say, "more surgical." Either method, however, is likely to produce an unharmed fetus. Lowrie, a technician of the first order, has invented two self-retaining retractors: one for abdominal or vaginal retraction, the other for the vulva. Many operations can thus be performed without an assistant or with minimal assistance. Moreover, no human body gets in the way of the operator if such retractors are used. The chapter on operations for relief of patients with intractable pain should be of special interest to all gynecologists. One who cannot cure but can bring relief to such patients will be highly praised.

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The Hormones: Physiology, Chemistry and Applications. Volume III. Edited by Gregory Pincus and Kenneth V. Thimann. Cloth. $22. Pp. 1012, with illustrations. Academic Press, Inc., 125 E. 23rd St., New York 10, 1955.

Like the preceding volumes, the first of which appeared seven years ago, the present compilation gives an up-to-date critical review of our present knowledge of the hormones. It not only supplements the preceding volumes by including details of recent experimental work, but also many of the chapters supplant outdated previous treatment of the same subjects. As in the earlier volumes, sections are devoted to such topics as plant growth hormones, hormones in invertebrates, and neurohormones, as well as to the chemistry and physiology of the mammalian endocrine glands. The final chapter is devoted to clinical endocrinology. The 25 contributors are well-known workers who are actively engaged in research in these fields, and they give an up-to-date, sound, and documented review of their subjects. Detailed bibliographies follow each chapter, and an author as well as a subject index is included. The book is well organized and printed. It should serve as an excellent textbook and reference volume for the experimental endocrinologist and research worker. Since the book is devoted primarily to the basic biological aspects of the subject, the general practitioner and the practicing endocrinologist will find little of immediate interest in the volume but should find it useful as a source of reference for specific experimental data.

Hearing Therapy for Children. By Alice Streng, M.A., Director, Exceptional Division, Wisconsin State College, Milwaukee, and others. Cloth. $6.75. Pp. 371, with illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16; 99 Great Russell St., London, W.C.1, England, 1955.

This volume deals with the testing, management, and rehabilitation of the child with defective hearing. It is not always apparent whether a very young child hears well or, for that matter, hears at all. The authors suggest procedures for testing the hearing of the child who is too young to talk, such as the use of the psychogalvanic skin response audiometer. They tell how to select a hearing aid for a child and how to get the child to wear it. They have collected information from reliable sources as indicated by the bibliography, and it is unfortunate that the index is not up to the same high standard as the text. The book was evidently published before the Council on Physical Medicine and Rehabilitation discontinued its acceptance program. The various responsibilities in the education of the child with defective hearing on the part of the physician, the public health nurse, the speech and hearing therapist, the social worker, and the school administrator are outlined. The volume should find a place on the shelves of hearing rehabilitation centers, clinics for crippled children, and the offices of hearing-aid salesmen.

Treatment in Psychiatry. By Oskar Diethelm, M.D., Professor of Psychiatry, Cornell University Medical College, New York City. Third edition. Cloth. $9.50. Pp. 545. Charles C Thomas, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 49 Broad St., Oxford, England; The Ryerson Press, 299 Queen St., W., Toronto, 2B, Canada, 1955.

The new edition of this book, first published in 1936, carries forward Adolph Meyer's basic principles, modified by the influence of research and therapeutic experience. Meyer and Freud both regarded mental illness as the result of the patient's difficulty in dealing with his environment. Freud went further in his development of the concepts of the unconscious and of infantile sexuality and contributed a carefully organized technique of therapy called psychoanalysis. The author's main objective appears to be a presentation of a likewise-structured therapeutic approach now called "dynamic psychotherapy," replacing the cumbersome term "distributive analysis and synthesis" used in the previous editions. His avowed point of view is eclectic, i. e., the purposeful use of any therapeutic procedure, physical or psychological, that will aid the search for constructive solutions that fit the patient and his problems. Dynamic psychotherapy is "an analysis along selected dynamic lines and life situations," the dynamic factors including any psychological, psychopathological, physical, or environmental component. After briefly reviewing the various current theories and methods of psychotherapy, the author devotes an entire chapter to a discussion of psychoanalytic procedure. A rather detailed description is presented of pharmacological and physical methods of therapy, including insulin hypoglycemia, electroshock, narcosis, and lobotomy. Under chapter headings of different reaction types, the author elaborates on the application and special adaptations of previously described therapies. In the final chapter, he briefly reports on current progress and trends in psychiatric treatment, such as the use of chlorpromazine and Rauwolfia serpentina.

This book is clearly written, orderly, and presents many carefully condensed case histories with long-term follow-up reports. The chapters devoted to the discussion of the treatment of alcoholism and drug addiction are particularly praiseworthy. Relatively few of the bibliographic references were to recent literature. The nomenclature is not that adopted by the American Psychiatric Association in 1952. The author, contrary to most other investigators, still considers fever therapy the treatment of choice in paresis. His discussion of group therapy is far too brief, and there is no consideration of therapy in wartime psychiatry. Aside from these criticisms, the book is well worth careful reading by all psychiatrists and is an excellent source for the student and general physician looking for easily comprehended methods of therapy in psychiatry.

Journées internationales de médecine sportive militaire, 21-25 juin 1954. La nage en surface et sous-marine appliquée aux nécessités de la Marine militaire. Conseil international des sports militaires, semaine de la mer, Académie navale, Livorno. Supplément de la revue "Annali di medicina navale e tropicale." Paper. Pp. 176, with illustrations. Bureau sportif de la Marine militaire italienne. Direction générale de la santé militaire maritime, Rome, Italy, 1955.

This book contains 13 communications delivered at an international congress on the medical aspects of military athletics. The various authors discuss different aspects of aquatic activity: the maintenance of pools used for the instruction of swimmers and divers, the symptoms and mechanism of oxygen intoxication, nervous reactions to immersion, the optical effects of immersing the cornea, hemodynamic and other phenomena noted in underwater swimming, problems of shipwreck, rescue, and resuscitation, and the analysis of accidents (especially regarding decompression sickness) to swimmers and divers. All the contributions are written in compact style, and each is followed by a bibliography not only showing good knowledge of American work but also affording a valuable key to current European publications. This book deserves the attention of every physiologist and is recommended to physicians who deal with swimmers and divers.

Adoption . . . and After. By Louise Raymond. Foreword by Sidonie M. Gruenberg. Cloth. $3. Pp. 238. Harper & Brothers, 49 E. 33rd St., New York 16, 1955.

Understanding and warmth of presentation make this volume desirable reading for couples interested in adopting a child but lacking basic information and guidance about how to proceed. The author draws on her own experience with adoption procedures and uses a wide variety of authoritative data obtained from various professional groups. After preliminary counseling on self-examination by prospective parents, which frequently is overlooked or done too superficially, good advice is given in a chapter on what can be expected to be known about the child. As the author points out, adoption should not be a blind procedure, but at the same time there are no absolute tests that will guarantee perfect results in all cases. The rest of the book deals with various aspects of life with the adopted child. Good advice is provided about telling the child he is adopted, what sort of reaction can be expected, and how to handle it. Matters such as other children in the family, adoption of an older child, and what to do about special problems are considered at length. Because the book includes an extensive list by states of adoption agencies, it is a real working tool. Books for collateral reading are suggested also. This book may well be of interest and assistance to many physicians to whom couples often go in their faltering search for a child.

QUERIES AND MINOR NOTES

HEREDITARY OPTIC ATROPHY

To the Editor:—*A 17-year-old white girl has hereditary pigment degeneration of the retina (typical "bone corpuscle pigment," waxy yellow optic atrophy, constricted visual fields, and hemeralopia). The serology is negative. One sibling is also affected. The patient's vision is 20/200. Is the ocular condition an absolute indication for interruption of her pregnancy? (1) By reason of possible acceleration of oncoming blindness of the mother? (2) By reason of possible pigment degeneration in the child, if there is no consanguinity and if the father is a fifth cousin with no known pigment degeneration in his family?* *M.D., Ohio.*

This inquiry was referred to three consultants, whose respective replies follow.—Ed.

Answer.—The serious aggravation of constitutional retinal pigmentary degeneration by normal pregnancy and labor is rare unless there is potential or actual complicating disease. As these conditions cannot usually be foretold, the possibility of further sight loss must be considered. The information given is insufficient to determine the exact genetic method of transmission and the risks involved to the offspring. Obviously, every potential and actual aggravating disease to the mother should be diagnosed and treated, and a genetic survey should be made to determine the method of transmission and the risks involved to the potential offspring. The prompt termination of pregnancy, however, is fully justified in this case by (1) the risk of aggravation to the mother's already defective sight, (2) the progressive course of the disease in this case, and (3) the risk of transmission to the unborn child and its progeny.

Answer.—Pregnancy has no deleterious effect upon the progress of hereditary optic atrophy. Consequently its interruption is not indicated in the interest of the mother's condition. Hereditary optic atrophy may be a dominant trait, a recessive one, or a sex-linked one. It would be necessary to determine the mode of inheritance of the condition before it would be possible to state, with any reasonable degree of accuracy, the chance that the unborn child will be affected. This means that the eyes of many of the relatives should be examined, even though they may not have grossly defective vision. The eyes of these relatives may exhibit only slight but definite characteristics of the defect (Snyder, L. H.: Clinical and Social Aspects of Heredity in Ophthalmology, Acta XVI Concilium Ophthalmologicum [Britannia] 1950). Even though a genetic study of the family might suggest that the unborn child is very likely to be affected, there would still be a chance that it would be normal. In view of the latter possibility there will still be a difference of opinion as to whether therapeutic abortion is indicated. It is currently believed that a committee of specialists should review all evidence before any therapeutic abortion is undertaken. This case raises the question as to whether a pregnancy should be terminated in order to prevent the birth of a child who is likely to exhibit any serious congenital defect. For a comprehensive review of current thinking upon the whole problem of therapeutic abortion, from the ethical, as well as from the medical point of view, a volume has been published recently on this subject (Rosen, H.: Therapeutic Abortion: Medical, Psychiatric, Anthropological and Religious Considerations, New York, the Julian Press, 1954).

Answer.—Duke-Elder, in his "Textbook of Ophthalmology" (volume 3, St. Louis, C. V. Mosby Company, 1941), says: "Since Liebreich (1861) drew attention to the prevalence of pigmentary degeneration of the retina in certain families and discovered that the subjects of the disease were often the children of cousins, the hereditary aspects of this condition have excited a very great deal of interest and have stimulated an enormous literature. The most authoritative study of the early literature and collection of data was provided by Nettleship (1907-08) who found in 976 families in which the disease occurred evidence of its herditary transmission in about half the cases, without consanguinity in 230 instances (23.5%), with consanguinity in 226 (23%), and with both heredity and consanguinity in 32 (3.5%). A further elaborate study of 40 pedigrees was made by Usher (1913), and a survey of the literature by Bell (1922). Indeed, so frequently is it hereditary that it can be accepted as certain that it is so in many cases where proof is wanting and superficial questioning reveals no indications of its incidence in the immediate precedents." Duke-Elder also says: "From the eugenic point of view the important fact emerges that no reliable advice can be given as to the possibility of transmission to the next generation until the nature of the pedigree has been worked out in each individual case. When it appears as a dominant characteristic each affected individual gets the disease directly from one parent and the chances are that it will be passed on to half the children. Unless it is considered right to produce children who will eventually become blind, these people should have none. When it appears a simple recessive the prohibition of inter-marriages within the same pedigree or into a family carrying the trait becomes imperative, and if they do occur they should be sterile. When it is inherited as a recessive sex-linked character half the sisters and all the daughters of the affected man will tend to pass the disease to half their sons; the responsibility therefore rests upon the women of the family. The determining factor in the incidence of primary pigmentary degeneration is heredity, and owing to the proportion of sex-linked cases, males are more frequently affected than females."

CARBON MONOXIDE POISONING DURING PREGNANCY

To the Editor:—*A 30-year-old white married woman had two healthy children, ages 6 and 3, after unremarkable pregnancies and deliveries. She has just finished her first trimester of a third pregnancy, and has been spotting throughout the last month. During the last two months she has been exposed to carbon monoxide in amounts sufficient to cause the entire family to complain of headaches and nausea. Can this amount of carbon monoxide cause the staining? Can carbon monoxide in amounts insufficient to cause unconsciousness do damage to the fetus? Can it cause fetal death and/or abortion?*

Isidore M. Goodman, M.D., Brooklyn, N. Y.

Answer.—Because of the confusion in the literature about the passage of carbon monoxide across the placenta from maternal to fetal blood, Curtis and co-workers (*A. M. A. Arch. Path.* **59**:677 [June] 1955) reviewed the literature and performed animal experiments. They found 20 cases of carbon monoxide poisoning during pregnancy and proof that carbon monoxide does pass from the maternal to the fetal circulation. The percentage of saturation of fetal hemoglobin with carbon monoxide is dependent upon the percentage of saturation of the mother's hemoglobin with carbon monoxide and the length of time of exposure to the gas. The saturation of fetal hemoglobin with carbon monoxide lags significantly behind the saturation of the maternal hemoglobin, owing to the slow dissociation of maternal carboxyhemoglobin. After a period of time an equilibrium is approached between fetal and maternal blood. In a few instances the infants later showed cerebral disorders. In view of the foregoing study it is possible for the fetus in the case cited to have been affected. However, the chances for any permanent damage are not great. If the fetus dies in utero from the carbon monoxide, an abortion will usually follow.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

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SLIPPED INTERVERTEBRAL DISKS

To the Editor:—*Kindly give information on the operation for slipped intervertebral disks. The region involved is the lumbar. I am mainly interested in the percentages of relief and cures for this surgery when done by orthopedic surgeons.*

M.D., Michigan.

Answer.—Recently published series of cases have indicated that an increasing number of surgeons favor a combined procedure of removal of the disk and spinal fusion, providing the spinal fusion can be successful in a high percentage of cases. Myelograms, for diagnostic purposes, are of questionable value. They do not decide whether or not an operation should be done. Careful examination at the time of operation will disclose more information than can be obtained by any myelogram. In the hands of a skilled orthopedic surgeon, there will be considerable variation in the success of operative procedure depending on the type of fusion performed and, the most important factor, the location of the defective disk. A herniation of the fifth lumbar disk, subjected to an excision of the disk and curettement of the disk space followed by an adequate posterior fusion or a combined interbody and posterior fusion, should and does result in close to 100% success. Fusion procedures between the fourth and fifth lumbar vertebrae are much more difficult because of the structural instability. When, as a result of degenerative changes, acute trauma, or repeated minimal trauma, an intervertebral disk suffers a disruption of its mechanical integrity to such a degree that there is impingement of the disk substance on the nerve roots in the spinal canal or irritation of the sensory nerves in the annulus fibrosis, the symptoms produced are said to be due to a slipped intervertebral disk. There are a number of other names for this condition. There is wide diversity of opinion as to the character of the operation that should be done in these cases. If they have failed to respond to adequate conservative treatment, the neurosurgeons for the most part, simply remove the disk. A removal and curettage of the fourth disk space, followed by an adequate interbody fusion combined with a posterior fusion that includes intrinsic internal autogenous bone graft fixation of the articular facets combined with a central prop of maximal strength should, at this level, produce in excess of 90% good results.

RECURRENT SKIN INFECTIONS

To the Editor:—*An 18-year-old boy has had three attacks of erysipelas of the right thigh during the past four months. He has responded well each time to 600,000 units of penicillin daily intramuscularly, for about four doses. He has no evidence of epidermophytosis or any kind of infection on his entire lower extremities. He has, however, enlarged tonsils that have large crypts; pus may be pressed out of both tonsils. He also has poor oral hygiene and several bad teeth. Do you think a tonsillectomy and extraction of the bad teeth would help clear up the erysipelas?*

T. N. Humphrey, M.D., Selmer, Tenn.

Answer.—In this instance one must question the diagnosis of erysipelas, which is a hemolytic Streptococcus infection of the skin and for which there should be a local atrium of infection. Some other type of skin inflammation should be suspected. If the tonsils are badly infected, as suggested by the questioner, and the teeth show areas of rarefaction at their roots, one could hardly make any mistake in removing these foci of infection. However, their relation to the erysipelas-like lesions of the thigh is questionable. Ordinarily the skin manifestations resulting from hemolytic Streptococcus infections of the tonsils would be more diffuse. If the lesion in question responds to penicillin, it should, of course, be treated with this antibiotic again. If the erysipelas recurs, an attempt might be made to confirm the diagnosis by making a needle puncture into the skin near the edge of the lesion, then injecting sterile saline solution into the skin about 4 to 5 mm. away and drawing up some of the saline solution that exudes through the first needle puncture for culture on blood agar. Often hemolytic streptococci may be cultured from the edge of the advancing erysipelas lesion in this way.

VARICOSE VEINS

To the Editor:—*What is the present attitude on treatment of varicose veins with injectable sclerosing agents?*

L. Edward Giovine, M.D., Woodside, N. Y.

Answer.—The injection treatment of varicose veins was popular in the 1920's and still has some staunch adherents. However it became obvious in the early 1930's that the increased venous pressure that results from the overflow from the deep venous system through incompetent saphenous and perforator valves soon recanalizes the obliterated venous segments. Worse than that the obliteration of dilated segments often produces other dilatations, thus scattering the varices, as long as their connection with the feeding systems is not interrupted. For this reason, the multiple ligations and stripping procedures have certainly displaced the sclerosing therapy in most institutions. Following an extensive stripping of the long and short saphenous vein and the individual ligation of perforators, a few distended varicosities may remain. These are injected in one sitting about two weeks after operation to complete the treatment.

CHANGES IN URINE FOLLOWING PAS THERAPY

To the Editor:—*Please discuss chemical changes in the urine of tuberculous patients who receive sodium* p*-aminosalicylic acid. We have consistently encountered atypical reactions for urobilinogen in these patients.*

Arthur Hirsch, M.D., Woodbine, N. J.

Answer.—Most clinical tests for urobilinogen involve the use of Ehrlich's aldehyde reagent (*p*-dimethylaminobenzaldehyde). *p*-Aminosalicylic acid (PAS) also gives a strong color with this reagent, and in fact a number of colorimetric procedures for the determination of *p*-aminosalicylic acid are based upon the use of this reagent. It is known that a small amount of free *p*-aminosalicylic acid is excreted in human urine, and this might account for your "atypical" urobilinogen tests. Urine chemistry is essentially normal on continued administration of *p*-aminosalicylic acid with one striking exception. Several reports have appeared in the literature on the presence of reducing substances in urine following the administration of *p*-aminosalicylic acid. The causative agent has not been identified with certainty, but it appears to be associated with the presence of a glucuronic acid conjugate of *p*-aminosalicylic acid. This does not occur in all patients and may represent an alternate pathway of metabolism for the drug. The principal metabolite of *p*-aminosalicylic acid is the N-acetyl derivative, and a conjugate with glycine has also been described.

UNDESCENDED TESTICLE

To the Editor:—*What is the accepted therapy for an undescended left testicle in an otherwise well-developed, normal 3-year-old boy? The undescended testicle is not palpable in the inguinal canal, and there is no hernia present. Please specify kind and dose of hormone and if and when surgical therapy should be done.* *M.D., New York.*

Answer.—Unilateral undescended testis in an otherwise normal boy signifies congenital absence of the testis, hypoplastic testis that has failed to descend, a normal testis that has failed to descend because of abnormal attachments or obstruction at the internal ring, a migratory testis (pseudocryptorchidism), or an ectopic testis usually present somewhere in the perineal region outside of the inguinal canal. If the scrotum is underdeveloped on the side of the undescended testis, it means that in all probability the testis had never been in the scrotum and therefore usually eliminates the possibility of a migratory testis. If an ectopic testis has been excluded, the following management is recommended. No treatment is necessary until the boy is 6 to 8 years of age, at which time hormone therapy may be tried for the following reasons: if the testis is hypoplastic or underdeveloped, it may descend following hormonal stimulation; if the testis is migratory, hormone therapy results in a rapid, dramatic descent. If the testis is present and is unable to descend because of abnormal attachments or obstruction at the internal inguinal ring, hormone stimulation may cause swelling of the testis with pain or discomfort in the area, indicating its presence.

If a reasonable course of hormone therapy fails, then operative interventions should be done immediately thereafter to avoid secondary atrophy of a testis that may be present and brought down surgically and to determine whether or not a testis is present and under what circumstances. If a testis is present that cannot be placed in the scrotum by accepted surgical procedures, it should be removed, as atrophy will occur eventually and carcinoma may develop at a later age. If hormone therapy is attempted, the following is recommended: chorionic gonadotrophin, 500 to 1,000 I. U. three times weekly intramuscularly for a maximum of 12 injections in most instances.

ROENTGENOGRAMS TAKEN DURING PREGNANCY

To the Editor:—*What are the chances of injuries to the fetus if a series of x-rays are taken for an intravenous pyelogram in a young woman who is presumably one and a half to two months pregnant? Five roentgenograms were taken with a tube setting of 30 in. distance, 70 kv., and 100 ma. Duration of exposure was 1 second for each of the films.*

M.D., California.

Answer.—Greenhill's "Obstetrics," 11th edition, 1955, page 166, says: "Roentgenography for diagnostic purposes in obstetrics entails no risk. For each film exposure the maximal energy delivered into the vagina, as measured with an ionization chamber, is 2 r. When five film studies are made, which is the most complete type of study, about 7 r are delivered. This is well within the safety limit." While most roentgenologists hold the foregoing opinion, geneticists are very much worried about any use of x-rays for diagnostic purposes during pregnancy because of the harm that results from x-ray exposure to lower animals.

ODORS IN POORLY VENTILATED ROOMS

To the Editor:—*Please explain how to deal with odors in closed rooms with rather poor ventilation. The odors are of "organic" nature such as sweat. I have tried some commercial preparations dispersed by some modification of the electric current; these preparations have a penetrating boarding-house smell that is worse than the odor to be dealt with. Would Glycol vaporizers be of value for this purpose?*

M.D., New York.

Answer.—It is generally considered that odors from sweat are due not so much to volatile material originally present but to the action of bacteria and mold on perspiration. The general principles involved in control of such odors are (1) the removal of the source of the odor and (2) provision for proper ventilation. Instruments and materials for which claims are made concerning the removal of odors generally operate on the principle of dulling the sense of smell or through a masking action. Glycol vaporizers have not been shown to be of use in overcoming organic odors, e. g., sweat in stale air. The room containing the odor should have removed from it articles to which the odor is clinging, should then be thoroughly ventilated, and finally should be washed down with water containing disinfectant such as sodium hypochlorite and the quaternary ammonium compounds.

DISLOCATION OF TOE

To the Editor:—*Please discuss chronic nontraumatic dislocation of the second toe in older obese women.*

Ivan Gilbert, M.D., Terre Haute, Ind.

Answer.—Chronic nontraumatic dislocation of the second toe in older obese women is rare. The condition is probably more common in patients who have had longstanding mild rheumatoid arthritis. Whatever the etiology may be, it is not always sufficiently painful to require treatment. When the condition is painful, it is most effectively treated by excision of the proximal phalanx, that is, subperiosteal removal of the proximal phalanx of this toe. To prevent the toe from markedly shortening, it is advisable to make 3-mm. to 4-mm. incisions in the opposing contacting surfaces of the first toe and the second toe just proximal to the ends of these toes and suturing the two toes together.

HEMOGLOBIN VALUES

To the Editor:—*Are there any differences in hemoglobin standards (grams and per cent) between newborn infants, adults, and pregnant women?*

F. M. Dougherty, M.D., Pottsville, Pa.

Answer.—It is generally accepted that the use of per cent in expressing hemoglobin values is misleading, since there is a normal variation in values from one age to another, from one sex to another, and even normally from one individual to another. At birth the normal values for hemoglobin are high, usually in the range of 19 to 20 gm. per 100 cc. with occasionally even higher figures. This level decreases steadily to reach 12 to 14 gm. per 100 cc. at the end of three months (the so-called physiological anemia of infancy), and persists at this level for a year or slightly longer, rising slowly thereafter to attain a level of about 14 gm. per 100 cc. by the fourth or fifth year. There is little subsequent change in the hemoglobin level in females until pregnancy occurs. The male level rises at puberty to 15 to 16 gm. per 100 cc., where it stays throughout adulthood. During pregnancy the total blood volume gradually increases by one-fourth, so that by term the hemoglobin level drops about 15% below the so-called normal value. This decrease begins in the first trimester and produces what is apparently a normocytic but physiological anemia. Following delivery, the hemoglobin level returns to normal levels by the fifth or sixth month.

ANTABUSE THERAPY

To the Editor:—*We use Antabuse frequently in our cases of chronic alcoholism. Does Antabuse have any unfavorable effects in cases of peptic ulcer?* *M.D., Massachusetts.*

Answer.—Disulfiram (Antabuse) is in all probability a mild gastric irritant. When it is given experimentally to animals in large doses vomiting and diarrhea have been produced; at autopsy evidence of mucosal inflammation has been observed by Child and co-workers (*Am. J. Psychiat.* **107**:774, 1951). Gastrointestinal symptoms such as nausea, vomiting, abdominal cramps, diarrhea, and constipation are not uncommon in patients given Antabuse; however, these symptoms appear to be a function of dosage and usually can be controlled by regulation of the dose. No reports indicating that peptic ulcer is aggravated by doses of Antabuse have been found in the literature; there have been no reported studies on the effect of this drug on gastric secretion. Peptic ulcer is not a recognized contraindication to Antabuse therapy.

RECURRING PAROTITIS

To the Editor:—*A 7½-year-old boy has had recurrent swelling of the parotid glands since the age of 4. A maternal aunt has hay fever. The swellings are usually bilateral and occasionally unilateral and are, in some instances, of considerable size. These attacks have been associated with temperature up to 103 F (39.5 C). Roentgenograms revealed no opaque calculi or other abnormalities. Blood cell studies, including bone marrow, have been within normal limits. He has been treated with antibiotics, orally and intramuscularly and, administered, in addition, with autogenetic vaccine without much benefit. For a year, the recurrent bilateral swellings have persisted in spite of all these therapies. He has been referred for further investigation, at which time the parotid ducts were found to be patent following the introduction of a contrasting medium. What further can be offered this patient?*

Joseph H. Fries, M.D., Brooklyn, N. Y.

Answer.—The description of the condition present in this young patient fits in well with so-called recurrent swelling of the parotid gland or so-called recurring parotitis. The etiological basis of the condition is not known, and there has been no agreement regarding effective treatment. Perhaps the most hopeful aspect of the problem is that the condition ceases in a considerable number of patients during the teen-age period. A brief, but good, discussion is to be found in the *A. M. A. American Journal of Diseases of Children*, October, 1952, page 468.